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<p>(21) International Application Number: PCT/US93/07545 (22) International Filing Date: 11 August 1993 (11.08.93)  (30) Priority data: 07/925,460 11 August 1992 (11.08.92) US Not furnished 15 June 1993 (15.06.93) US  (71) Applicant: PRESIDENT AND FELLOWS OF HARVARD COLLEGE [US/US]; 17 Quincy Street, Cambridge, MA 02138 (US).  (72) Inventors: URBAN, Robert, Glen ; 76 Hatfield Road, Newton, MA 02165 (US). CHICZ, Roman, M. ; 82 Glen Road, Jamaica Plain, MA 02130 (US). VIGNALI, Dario, A. ; 761 Lower Rainham Road, Rainham, Kent ME8 7UB (GB). HEDLEY, Mary, Lynne ; 214 Walden Street, #1, Cambridge, MA 02140 (US). STERN, Lawrence, J. ; 181 Newport Street, Arlington, MA 02174 (US). STROMINGER, Jack, L. ; 2030 Massachusetts Avenue, Lexington, MA 02173 (US).</p>	<p>(74) Agent: CLARK, Paul, T.; Fish and Richardson, 225 Franklin Street, Boston, MA 02110-2804 (US).  (81) Designated States: CA, JP, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).  <b>Published</b> <i>With international search report.</i></p>	
<p>(54) Title: IMMUNOMODULATORY PEPTIDES</p> <p>(57) Abstract</p> <p>A purified preparation of a peptide consisting essentially of an amino acid sequence identical to that of a segment of a naturally-occurring human protein, said segment being of 10 to 30 residues in length, inclusive, wherein said peptide binds to a human major histocompatibility complex (MHC) class II allotype.</p>		

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IMMUNOMODULATORY PEPTIDES

This application is a continuation-in-part of co-pending USSN 07/925,460, filed August 11, 1992. The invention was made in the course of research funded in part by the U.S. Government under NIH Grant 5R35-CA47554; the U.S. Government therefore has certain rights in the invention.

The field of the invention is major histocompatibility complex (MHC) antigens.

Background of the Invention

Major histocompatibility complex (MHC) class II antigens are cell surface receptors that orchestrate all specific immune responses in vertebrates. Humans possess three distinct MHC class II isotypes: DR, for which approximately 70 different allotypes are known; DQ, for which 33 different allotypes are known; and DP, for which 47 different allotypes are known. Each individual bears two to four DR alleles, two DQ alleles, and two DP alleles.

MHC receptors (both class I and class II) participate in the obligate first step of immune recognition by binding small protein fragments (peptides) derived from pathogens or other non-host sources, and presenting these peptides to the regulatory cells (T cells) of the immune system. In the absence of MHC presentation, T cells are incapable of recognizing pathogenic material. Cells that express MHC class II receptors are termed antigen presenting cells (APC). APCs ingest pathogenic organisms and other foreign materials by enveloping them in endosomic vesicles, then subjecting them to enzymatic and chemical degradation. Foreign proteins which are ingested by APCs are partially degraded or "processed" to yield a mixture of peptides, some of which are bound by MHC class II molecules that

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are en route to the surface. Once on the cell surface, MHC-bound peptides are available for T cell recognition.

MHC class II antigens are expressed on the surface of APCs as a trimolecular complex composed of an  $\alpha$  chain, a  $\beta$  chain, and a processed peptide. Like most polypeptides that are expressed on the cell surface, both  $\alpha$  and  $\beta$  chains contain short signal sequences at their  $\text{NH}_2$  termini which target them to the endoplasmic reticulum (ER). Within the ER the class II  $\alpha/\beta$  chain complex associates with an additional protein termed the invariant chain (Ii). Association with Ii is proposed to block the premature acquisition of peptides (by blocking the peptide binding cleft of the MHC heterodimer), promote stable  $\alpha/\beta$  interaction, and direct subsequent intracellular trafficking of the complex to endosomal vesicles. In the endosomes, Ii is removed by a process involving proteolysis; this exposes the peptide binding cleft, thus allowing peptides present in the endosome to bind to the MHC molecule. The class II/ peptide complex is transported from the endosomes to the cell surface where it becomes accessible to T-cell recognition and subsequent activation of immune responses. Class II MHC molecules bind not only to peptides derived from exogenous (ingested) proteins, but also to those produced by degradation of endogenous (self) proteins. The amount of each species of peptide which binds class II is determined by its local concentration and its relative binding affinity for the given class II binding groove, with the various allotypes displaying different peptide-binding specificities.

Early during fetal development, the mammalian immune system is "tolerized", or taught not to react, to self-peptides. The stability and maintenance of this system is critical for ensuring that an animal does not generate an immune response against self. A breakdown of



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this system gives rise to autoimmune conditions such as diabetes, rheumatoid arthritis and multiple sclerosis. Current technologies intended to manipulate the immune system into reestablishing proper nonresponsiveness  
5 include protocols involving the intravenous delivery of synthetic, high affinity binding peptides as blocking peptides.

Vaccination can generate protective immunity against a pathogenic organism by stimulating an antibody-  
10 mediated and/or a T cell-mediated response. Most of the current vaccination strategies still use relatively crude preparations, such as attenuated or inactivated viruses. These vaccines often generate both antibody- and cell-mediated immunity, and do not allow one to modulate the  
15 type of immune response generated. Moreover, in many diseases the generation of the wrong type of response can result in an exacerbated disease state.

#### Summary of the Invention

In the work disclosed herein, naturally processed  
20 peptides bound to six of the some 70 known human MHC class II DR allotypes (HLA-DR1, HLA-DR2, HLA-DR3, HLA-DR4, HLA-DR7, and HLA-DR8) have been characterized. These peptides were found to be predominantly derived from self proteins rather than foreign proteins. Several  
25 self peptide families have been identified with the unexpected property of degenerate binding: that is, a given self-peptide will bind to a number of HLA-DR allotypes. This observation runs counter to the widely-accepted view of MHC class II function, which dictates  
30 that each allotype binds a different set of peptides. Furthermore, many if not all of the self-peptides disclosed herein bind to the class II molecules with relatively high affinity. These three characteristics--  
(1) self rather than foreign, (2) degeneracy, and (3)

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high affinity binding--suggest a novel means for therapeutic intervention in disease conditions characterized by autoreactivity, such as Type I diabetes, rheumatoid arthritis, and multiple sclerosis. In addition, such therapy could be used to reduce transplant rejection.

In the therapeutic methods of the invention, short peptides modelled on the high-affinity immunomodulating self peptides of the invention (which preferably are nonallelically restricted) are introduced into the APCs of a patient. Tissue typing to determine the particular class II alleles expressed by the patient may be unnecessary, as the peptides of the invention are bound by multiple class II isotypes. It may be useful to employ a "cocktail" of peptides, where complete degeneracy is lacking for individual peptides, i.e., where peptides binds to fewer than all allotypes; the cocktail provides overlapping binding specificity. Once in the APC, a peptide binds to the class II molecules with high affinity, thereby blocking the binding of immunogenic peptides which are responsible for the immune reaction characteristic of the disease condition. Because the blocking peptides of the invention are self peptides with the exact carboxy and amino termini tolerized during ontogeny, they are immunologically inert and will not induce an immune response which may complicate treatment using non-self blocking peptides.

The peptides of the invention may be introduced into APCs directly, e.g., by intravenous injection of a solution containing one or more of the peptides. Alternatively, the APCs may be provided with a means of synthesizing large quantities of the blocking peptides intracellularly. Recombinant genes that encode ER and/or endosomal targeting signals fused to blocking peptide sequences are linked to appropriate expression control

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sequences and introduced into APCs. Once in the cell, these genes direct the expression of the hybrid peptides. Peptides targeted to the ER will bind class II  $\alpha$  and  $\beta$  chains as they are translated and assembled into heterodimers. The presence of high affinity binding peptides within the ER will prevent association of the  $\alpha/\beta$  complex with invariant chain, and thus interfere with intracellular trafficking. The class II molecule/blocking peptide complex may subsequently be expressed on the cell surface, but would not elicit an immune response since T cells are tolerized to this complex early in development. The use of peptides tagged with ER retention signals may also prevent the peptide-complexed class II molecules from leaving the ER. Alternatively, the recombinant peptide may be tagged with an endosomal targeting signal which directs it to the endosomal compartment after synthesis, thereby also skewing the ratio of endogenously-processed peptide to blocking peptide in the endosome and favoring binding of the high affinity blocking peptide to any class II molecules which did not bind it in the ER. It may be advantageous, for any individual patient, to employ one or more ER-directed peptides in combination with one or more endosome-directed peptide, so that  $\alpha$ - $\beta$  complexes which are not filled in the ER with peptides of the invention are then blocked in the endocytic pathway. The end result again is cell surface expression of a non-immunogenic class II/peptide complex.

The use of a class II nonrestricted high affinity binding peptide coupled to an intracellular delivery system permits the specific down-regulation of class II restricted immune responses without invoking the pleiotropic adverse reactions associated with the current pharmacological strategies. Successful application of these technologies will constitute a significant advance

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towards the treatment of autoimmune disease and prevention of transplant rejection.

The intracellular delivery system of the invention can also be utilized in a novel method of vaccination of an animal, e.g., a human patient or a commercially significant mammal such as a cow which is susceptible to diseases such as hoof and mouth disease. Such a system can be tailored to generate the type of immune response required in a given situation by adjustments in the following: (a) peptide specificity for class I or class II MHC; (b) peptide/protein length and/or sequence, and (c) using specific tags for organelle targeting. The system of the invention ensures that peptides are produced only within cells, and are not present outside the cells where they could stimulate antibody production by contact with B cells. This limits the immune response generated by such a vaccine to T cell-mediated immunity, thereby preventing either an inappropriate or potentially deleterious response as might be observed with standard vaccines targeting the organisms which cause, for example, HIV, malaria, leprosy, and leishmaniasis. Furthermore, this exclusively T cell-mediated immune response can be class I or class II-based, or both, depending upon the length and character of the immunogenic peptides: MHC class I molecules are known to bind preferentially to peptides 8 to 10 residues in length, while class II molecules bind with high affinity to peptides that range from 12 to 25 residues long.

Immunization and therapy according to the invention can employ a purified preparation of a peptide of the invention, i.e., a peptide which includes an amino acid sequence identical to that of a segment of a naturally-occurring human protein (i.e., a "self protein"), such segment being of 10 to 30 residues in length, wherein the peptide binds to a human MHC class II

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allotype, and preferably binds to at least two distinct MHC class II allotypes (e.g., any of the approximately 70 known DR allotypes, approximately 47 known DP allotypes, or approximately 33 known DQ allotypes). The portion of the peptide corresponding to the self protein segment is herein termed a "self peptide". By "purified preparation" is meant a preparation at least 50% (by weight) of the polypeptide constituents of which consists of the peptide of the invention. In preferred embodiments, the peptide of the invention constitutes at least 60% (more preferably at least 80%) of the purified preparation. The naturally-occurring human protein is preferably HLA-A2 (as broadly defined below), HLA-A29, HLA-A30, HLA-B44, HLA-B51, HLA-Bw62, HLA-C, HLA-DP  $\beta$ -chain, HLA-DQ  $\alpha$ -chain, HLA-DQ  $\beta$ -chain, HLA-DQ3.2  $\beta$ -chain, HLA-DR  $\alpha$ -chain, HLA-DR  $\beta$ -chain, HLA-DR4  $\beta$ -chain, invariant chain (Ii), Ig kappa chain, Ig kappa chain C region, Ig heavy chain, Na<sup>+</sup>/K<sup>+</sup> ATPase, potassium channel protein, sodium channel protein, calcium release channel protein, complement C9, glucose-transport protein, CD35, CD45, CD75, vinculin, calgranulin B, kinase C  $\zeta$ -chain, integrin  $\beta$ -4 gp150, hemoglobin, tubulin  $\alpha$ -1 chain, myosin  $\beta$ -heavy chain,  $\alpha$ -enolase, transferrin, transferrin receptor, fibronectin receptor  $\alpha$ -chain, acetylcholine receptor, interleukin-8 receptor, interferon  $\alpha$ -receptor, interferon  $\gamma$ -receptor, calcitonin receptor, LAM (lymphocyte activation marker) Blast-1, LAR (leukocyte antigen-related) protein, LIF (leukemia inhibitory factor) receptor, 4F2 cell-surface antigen (a cell-surface antigen involved in normal and neoplastic growth) heavy chain, cystatin SN, VLA-4 (a cell surface heterodimer in the integrin superfamily of adhesion receptors), PAI-1 (plasminogen activator inhibitor-1), IP-30 (interferon- $\gamma$  induced protein), ICAM-2, carboxypeptidase E, thromboxane-A synthase, NADH-

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cytochrome-b5 reductase, c-myc transforming protein, K-ras transforming protein, MET kinase-related transforming protein, interferon-induced guanylate-binding protein, mannose-binding protein, apolipoprotein B-100, cathepsin C, cathepsin E, cathepsin S, Factor VIII, von Willebrand factor, metalloproteinase inhibitor 1 precursor, metalloproteinase inhibitor 2, plasminogen activator inhibitor-1, or heat shock cognate 71 kD protein; it may be an MHC class I or II antigen protein or any other human protein which occurs at the cell surface of APCs. The self peptide preferably conforms to the following motif: at a first reference position (I) at or within 12 residues of the amino terminal residue of the segment, a positively charged residue (i.e., Lys, Arg, or His) or a large hydrophobic residue (i.e., Phe, Trp, Leu, Ile, Met, Tyr, or Pro; and at position I+5, a hydrogen bond donor residue (i.e., Tyr, Asn, Gln, Cys, Asp, Glu, Arg, Ser, Trp, or Thr). In addition, the peptide may also be characterized as having, at positions I+9, I+1, and/or I-1, a hydrophobic residue (i.e., Phe, Trp, Leu, Ile, Met, Pro, Ala, Val, or Tyr) (+ denotes positions to the right, or toward the carboxy terminus, and - denotes positions to the left, or toward the amino terminus.) A typical peptide of the invention will include a sequence corresponding to residues 31-40 (i.e., TQFVRFDSDA; SEQ ID NO: 149) or residues 106-115 (i.e., DWRFLRGYHQ; SEQ ID NO: 150) of HLA-A2, or residues 107-116 (i.e., RMAPLLMQA; SEQ ID NO: 151) of Ii, or a sequence essentially identical to any one of the sequences set forth in Tables 1-10 below.

The therapeutic and immunization methods of the invention can also employ a nucleic acid molecule (RNA or DNA) encoding a peptide of the invention, but encoding less than all of the entire sequence of the self protein. The nucleic acid preferably encodes no substantial

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portion of the self protein other than the specified self peptide which binds to a MHC class II molecule, although it may optionally include a signal peptide or other trafficking sequence which was derived from the self protein (or from another protein). A trafficking sequence is an amino acid sequence which functions to control intracellular trafficking (directed movement from organelle to organelle or to the cell surface) of a polypeptide to which it is attached. Such trafficking sequences might traffic the polypeptide to ER, a lysosome, or an endosome, and include signal peptides (the amino terminal sequences which direct proteins into the ER during translation), ER retention peptides such as KDEL (SEQ ID NO: 152); and lysosome-targeting peptides such as KFERQ (SEQ ID NO: 153), QREFK (SEQ ID NO: 154), and other pentapeptides having Q flanked on one side by four residues selected from K, R, D, E, F, I, V, and L. An example of a signal peptide that is useful in the invention is a signal peptide substantially identical to that of an MHC subunit such as class II  $\alpha$  or  $\beta$ ; e.g., the signal peptide of MHC class II  $\alpha$  is contained in the sequence MAISGVPVLGFFIIAVLMSAQESWA (SEQ ID NO: 155). The signal peptide encoded by the nucleic acid of the invention may include only a portion (e.g., at least ten amino acid residues) of the specified 25 residue sequence, provided that portion is sufficient to cause trafficking of the polypeptide to the ER. In preferred embodiments, the nucleic acid of the invention encodes a second self peptide and a second trafficking sequence (which may be identical to or different than the first self peptide and first trafficking sequence), and it may encode additional self peptides and trafficking sequences as well. In still another variation on this aspect of the invention, the self peptide sequence (or a plurality of self peptide sequences arranged in tandem) is linked

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by a peptid bond to a substantially intact Ii polypeptide, which then carries the self peptide sequence along as it traffics the class II molecule from ER to endosome.

5           The nucleic acid of the invention may also contain expression control sequences (defined as transcription and translation start signals, promoters, and enhancers which permit and/or optimize expression of the coding sequence with which they are associated) and/or genomic  
10 nucleic acid of a phage or a virus, such as an attenuated or non-replicative, non-virulent form of vaccinia virus, adenovirus, Epstein-Barr virus, or a retrovirus.

          The peptides and nucleic acids of the invention may be prepared for therapeutic use by suspending them  
15 directly in a pharmaceutically acceptable carrier, or by encapsulating them in liposomes, immune-stimulating complexes (ISCOMS), or the like. Such preparations are useful for inhibiting an immune response in a human patient, by contacting a plurality of the patient's APCs  
20 with the therapeutic preparation and thereby introducing the peptide or nucleic acid into the APCs.

          Also within the invention is a cell (e.g., a tissue culture cell or a cell, such as a B cell or APC, within a human) containing the nucleic acid molecule of  
25 the invention. A cultured cell containing the nucleic acid of the invention may be used to manufacture the peptide of the invention, in a method which involves culturing the cell under conditions permitting expression of the peptide from the nucleic acid molecule.

30           Disclosed herein is a method of identifying a nonallelically restricted immunomodulating peptide, which method includes the steps of:

          (a) fractionating a mixture of peptides eluted from a first MHC class II allotype;



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(b) identifying a self peptide from this mixture;  
and

(c) testing whether the self peptide binds to a second MHC class II allotype, such binding being an indication that the self peptide is a nonallelically restricted immunomodulating peptide.

In further embodiments, the invention includes a method of identifying a potential immunomodulating peptide, in a method including the steps of:

10 (a) providing a cell expressing MHC class II molecules on its surface;

(b) introducing into the cell a nucleic acid encoding a candidate peptide; and

(c) determining whether the proportion of  
15 class II molecules which are bound to the candidate peptide is increased in the presence of the nucleic acid compared to the proportion bound in the absence of the nucleic acid, such an increase being an indication that the candidate peptide is a potential immunomodulating  
20 peptide.

Also within the invention is a method of identifying a potential immunomodulating peptide, which method includes the steps of:

(a) providing a cell expressing MHC class II  
25 molecules on its surface;

(b) introducing into the cell a nucleic acid encoding a candidate peptide; and

(c) determining whether the level of MHC class II molecules on the surface of the cell is decreased in the  
30 presence of the nucleic acid compared to the level of MHC class II molecules in the absence of the nucleic acid, such a decrease being an indication that the candidate peptide is a potential immunomodulating peptide.

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Also included in the invention is a method of identifying a nonallelically restricted immunostimulating peptide, which method includes the steps of:

- (a) providing a cell bearing a first MHC class I or class II allotype, such cell being infected with a pathogen (e.g., an infective agent which causes human or animal disease, such as human immunodeficiency virus (HIV), hepatitis B virus, measles virus, rubella virus, influenza virus, rabies virus, *Corynebacterium diphtheriae*, *Bordetella pertussis*, *Plasmodium spp.*, *Schistosoma spp.*, *Leishmania spp.*, *Trypanasoma spp.*, or *Mycobacterium lepre*);
- (b) eluting a mixture of peptides bound to the cell's first MHC allotype;
- (c) identifying a candidate peptide from the mixture, such candidate peptide being a fragment of a protein from the pathogen; and
- (d) testing whether the candidate peptide binds to a second MHC allotype, such binding being an indication that the candidate peptide is a nonallelically restricted immunostimulating peptide. A nucleic acid encoding such an immunogenic fragment of a protein of a pathogen can be used in a method of inducing an immune response in a human patient, which method involves introducing the nucleic acid into an APC of the patient.

The therapeutic methods of the invention solve certain problems associated with prior art methods involving intravenous injection of synthetic peptides:

- (1) because of allelic specificity, a peptide capable of binding with high affinity to all, or even most, of the different class II allotypes expressed within the general population had not previously been identified; (2) the half-lives of peptides delivered intravenously are generally very low, necessitating repeated administration

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with the associated high level of inconvenience and cost;  
(3) this type of delivery approach requires that the  
blocking peptide displace the naturally-occurring peptide  
occupying the binding cleft of a class II molecule while  
5 the latter is on the cell surface, which is now believed  
to be a very inefficient process; and (4) if the blocking  
peptide utilized is itself immunogenic, it may promote  
deleterious immune responses in some patients.

Other features and advantages of the invention  
10 will be apparent from the following detailed description,  
and from the claims.

#### Detailed Description

The drawings are first briefly described.

#### Drawings

15 Figs. 1A-1F are chromatographic analyses of the  
peptide pools extracted from papain digested HLA-DR1,  
DR2, DR3, DR4, DR7, and DR8, respectively, illustrating  
the peptide repertoire of each HLA-DR as detected by UV  
absorbance. The UV absorbance for both 210 nm and 277 nm  
20 is shown at a full scale absorbance of 500 mAU with a  
retention window between 16 minutes and 90 minutes (each  
mark represents 2 minutes).

Fig. 2 is a representative mass spectrometric  
analysis of the size distribution of isolated HLA-DR1  
25 bound peptides. The determined peptide masses in groups  
of 100 mass units were plotted against the number of  
isolated peptides identified by mass spectrometry.  
Peptide length was calculated by dividing the  
experimental mass by an average amino acid mass of 118  
30 daltons.

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Fig. 3A is a representation of a minigen f the invention (SEQ ID NO: 147), in which the HLA-DR $\alpha$  chain leader peptide is linked to the amino terminus of a 15-residue blocking peptide fragment of human invariant chain Ii.

Fig. 3B is a representation of a second minigene of the invention (SEQ ID NO: 148), in which the HLA-DR $\alpha$  chain leader peptide is linked to the amino terminus of a 24-residue blocking peptide fragment of human invariant chain Ii.

### Experimental Data

#### METHODS

##### I. Purification of HLA-DR antigens.

HLA-DR molecules were purified from homozygous, Epstein-Barr virus-transformed, human B lymphoblastoid lines: DR1 from LG-2 cells, DR2 from MST cells, DR3 from WT20 cells, DR4 from Priess cells, DR7 from Mann cells, and DR8 from 23.1 cells. All of these cell lines are publicly available. Cell growth, harvest conditions and protein purification were as previously described (Gorga, J. et al., 1991). Briefly, 200 grams of each cell type was resuspended in 10mM Tris-HCl, 1mM dithiothreitol (DTT), 0.1mM phenylmethylsulfonylflouride (PMSF), pH 8.0, and lysed in a Thomas homogenizer. The nuclei were removed by centrifugation at 4000xg for 5 min and the pellets washed and repelleted until the supernatants were clear. All the supernatants were pooled and the membrane fraction harvested by centrifugation at 175,000xg for 40 min. The pellets were then resuspended in 10 mM Tris-HCl, 1mM DTT, 1mM PMSF, 4% NP-40. The unsolubilized membrane material was removed by centrifugation at 175,000xg for 2 hours, and the NP-40 soluble supernatant fraction used in immunoaffinity purification.

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Detergent soluble HLA-DR was bound to a LB3.1-protein A sepharose column (Gorga et al., *id*) and eluted with 100 mM glycine, pH 11.5. Following elution, the sample was immediately neutralized by the addition of 5 Tris-HCl and then dialyzed against 10mM Tris-HCl, 0.1% deoxycholic acid (DOC). The LB3.1 monoclonal antibody recognizes a conformational determinant present on the nonpolymorphic HLA-DR $\alpha$  chain, and thus recognizes all allotypes of HLA-DR.

10 The transmembrane domain of the DR molecules was removed by papain digestion, and the resulting water-soluble molecule further purified by gel filtration chromatography on an S-200 column equilibrated in 10mM Tris-HCl, pH 8.0. The purified DR samples were 15 concentrated by ultrafiltration, yield determined by BCA assay, and analyzed by SDS polyacrylamide gel electrophoresis.

## II. Extraction and fractionation of bound peptides.

Water-soluble, immunoaffinity-purified class II 20 molecules were further purified by high-performance size exclusion chromatography (SEC), in 25 mM N-morpholino ethane sulfonic acid (MES) pH 6.5 and a flowrate of 1 ml/min., to remove any residual small molecular weight contaminants. Next, Centricon microconcentrators 25 (molecular weight cutoff 10,000 daltons) (Amicon Corp.) were sequentially washed using SEC buffer and 10% acetic acid prior to spin-concentration of the protein sample (final volume between 100-200  $\mu$ l). Peptide pools were extracted from chosen class II alleles by the addition of 30 1 ml of 10% acetic acid for 15 minutes at 70°C. These conditions are sufficient to free bound peptide from class II molecules, yet mild enough to avoid peptide degradation. The peptide pool was separated from the class II molecule after centrifugation through the

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Centricon concentrator, with the flow-through containing the previously bound peptides.

The collected acid-extracted peptide pool was concentrated in a Savant Speed-Vac to a volume of 50  $\mu$ l prior to HPLC separation. Peptides were separated on a microbore C-18 reversed-phase chromatography (RPC) column (Vydac) utilizing the following non-linear gradient protocol at a constant flowrate of 0.15 ml/min.: 0-63 min. 5%-33% buffer B; 63-95 min. 33%-60% buffer B; 95-105 min 60%-80% buffer B, where buffer A was 0.06% trifluoroacetic acid/water and buffer B was 0.055% trifluoroacetic acid/acetonitrile. Chromatographic analysis was monitored at multiple UV wavelengths (210, 254, 277, and 292 nm) simultaneously, permitting spectrophotometric evaluation prior to mass and sequence analyses. Shown in Fig.1 are chromatograms for each of the six DR peptide pools analyzed. Collected fractions were subsequently analyzed by mass spectrometry and Edman sequencing.

### 20 III. Analysis of peptides.

The spectrophotometric evaluation of the peptides during RPC provides valuable information regarding amino acid composition (contribution of aromatic amino acids) and is used as a screening method for subsequent characterization. Appropriate fractions collected during the RPC separation were next analyzed using a Finnegan-MAT LaserMat matrix-assisted laser-desorption mass spectrometer (MALD-MS) to determine the individual mass values for the predominant peptides. Between 1%-4% of the collected fraction was mixed with matrix (1  $\mu$ l  $\alpha$ -Cyano-4-hydroxycinnamic acid) to achieve mass determination of extracted peptides. The result of this analysis for HLA-DR1 is shown in Fig. 2. Next, chosen peptide samples were sequenced by automated Edman

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degradation microsequencing using an ABI 477A protein sequencer (Applied Biosystems) with carboxy-terminal verification provided by mass spectral analysis using the Finnigan-MAT TSQ 700 triple quadrupole mass spectrometer  
5 equipped with an electro-spray ion source. This parallel analysis ensures complete identity of peptide composition and sequence. Peptide alignment with protein sequences stored in the SWISS-PROT database was performed using the FASTA computer database search program. Set forth in  
10 Tables 1-10 are the results of this sequence analysis for each of the DR molecules studied.

## RESULTS

### I. HLA-DR1.

The HLA-DR1 used in this study was papain  
15 solubilized to enable the material to be used both for crystallographic and bound peptide analyses. The peptides bound to DR1 were acid extracted and fractionated using RPC (Fig. 1). The absence of any detectable peptidic material following a second  
20 extraction/RPC separation verified quantitative peptide extraction. Amino acid analysis (ABI 420A/130A derivatizer/HPLC) of extracted peptide pools demonstrated a 70-80% yield, assuming total occupancy of purified DR1 with a molar equivalent of bound peptides corresponding  
25 to the size distribution determined by mass spectrometry (see Fig. 2). The RPC profiles obtained from DR1 extractions of multiple independent preparations were reproducible. Furthermore, profiles from either detergent-soluble or papain-solubilized DR1 were  
30 equivalent. To confirm that the peptides were in fact identical in detergent-soluble and papain-digested DR1, mass spectrometry and Edman sequencing analyses were performed and revealed identical masses and sequences for analogous fractions from the two preparations.

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Matrix-assisted laser desorption mass spectrometry (MALD-MS) was used to identify 111 species of unique mass contained within the eluted peptide pool of DR1 with an average size of 18 and a mode of 15 residues (Fig. 2).

5 Over 500 additional mass species present within the molecular weight range of 13-25 residues were detected; however, the signal was not sufficient to assign individual masses with confidence. Multiple species of varying mass were detected in fractions corresponding to single RPC

10 peaks indicating co-elution of peptides. To characterize these peptides further, samples were analyzed in parallel on a triple quadrupole mass spectrometer equipped with an electrospray ion source (ESI-MS) and by automated Edman degradation microsequencing (Lane et al., J. Prot. Chem.

15 10:151-160 (1991)). Combining these two techniques permits crucial verification of both the N- and C-terminal amino acids of peptides contained in single fractions. The sequence and mass data acquired for twenty peptides isolated from DR1 are listed in Table 1. All the

20 identified peptides aligned with complete identity to regions of proteins stored in the SWISS-PROT database.

Surprisingly, sixteen of the twenty sequenced DR1-bound peptides were 100% identical to regions of the self proteins HLA-A2 and class II-associated invariant chain

25 (Ii), representing at least 26% of the total extracted peptide mass. These isolated peptides varied in length and were truncated at both the N- and C-termini, suggesting that: 1) antigen processing occurs from both ends after binding to DR1, or 2) class II molecules bind antigen from

30 a pool of randomly generated peptides. The yields from the peptide microsequencing indicated that HLA-A2 (Fig. 1) and Ii each represents at least 13% of the total DR1-bound peptides.

An additional surprising finding concerned a peptide

35 which, although bound to HLA-DR and 100% homologous with



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HLA-A2 peptide, was derived from a cell which does not express HLA-A2 protein. Evidently this peptide is derived from a protein containing a region homologous with a region of HLA-A2 protein. Thus, for purposes of this specification, the term "HLA-A2 protein" is intended to include HLA-A2 protein itself, as well as any naturally occurring protein which contains a ten or greater amino acid long region of >80% homology with an HLA-DR-binding peptide derived from HLA-A2. An "HLA-A2 peptide" similarly refers to peptides from any HLA-A2 protein, as broadly defined herein.

The other four peptides identified in the DR1 studies were derived from two self proteins, transferrin receptor and the  $\text{Na}^+/\text{K}^+$  ATPase, and one exogenous protein, bovine serum fetuin (a protein present in the serum used to fortify the medium which bathes the cells). Each of these peptides occupied only 0.3-0.6% of the total DR1 population, significantly less than either the HLA-A2 or the Ii peptides. It is known that class II molecules en route to the cell surface intersect the pathway of incoming endocytic vesicles. Both recycling membrane proteins and endocytosed exogenous protein travel this common pathway. Hence, the HLA-A2, transferrin receptor,  $\text{Na}^+/\text{K}^+$  ATPase and bovine fetuin derived peptides would all encounter DR1 in a similar manner. Ii associates with nascent class II molecules in the endoplasmic reticulum (ER) (Jones et al., Mol. Immunol. 16:51-60 (1978)), preventing antigen binding until the class II/Ii complex arrives at an endocytic compartment (Roche and Cresswell, Nature 345:615-618 (1990)), where Ii undergoes proteolysis (Thomas et al., J. Immunol. 140:2670-2675 (1988); Roche and Cresswell, Proc. Natl. Acad. Sci. USA 88:3150-3154 (1991)), thus allowing peptide binding to proceed. Presumably, the Ii peptides bound to DR1 were generated at this step.

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Synthetic peptides corresponding to five of the peptides reported in Table 1 were made and their relative binding affinities to DR1 determined. The influenza A hemagglutinin peptide (HA) 307-319 (SEQ ID NO: 24) has been previously described as a high affinity, HLA-DR1 restricted peptide (Roche and Cresswell, J. Immunol. 144:1849-1856 (1990); Rothbard et al., Cell 52:515-523 (1988)), and was thus chosen as the control peptide. "Empty" DR1 purified from insect cells expressing recombinant DR1 cDNA was used in the binding experiments because of its higher binding capacity and 10-fold faster association kinetics than DR1 isolated from human cells (Stern and Wiley, Cell 68:465-477 (1992)). All the synthetic peptides were found to compete well ( $K_i < 100$  nM) against the HA peptide (Table 2). At first approximation, the Ii 106-119 peptide (SEQ ID NO: 156) had the highest affinity of all the competitor peptides measured, equivalent to that determined for the control HA peptide. In addition to the  $K_i$  determinations, these peptides were found to confer resistance to SDS-induced  $\alpha$ - $\beta$  chain dissociation of "empty" DR1 when analyzed by SDS-PAGE, indicative of stable peptide binding (Sadegh-Nasseri and Germain, Nature 353:167-170 (1991); Dornmair et al., Cold Spring Harbor Symp. Quant. Biol. 54:409-415 (1989); Springer et al., J. Biol. Chem. 252:6201-6207 (1977)). Neither of the two control peptides,  $\beta_2m$  52-64 (SEQ ID NO: 26) nor Ii 96-110 (SEQ ID NO: 25), was able to either confer resistance to SDS-induced chain dissociation of DR1 or compete with HA 307-319 (SEQ ID NO: 24) for binding to DR1; both of these peptides lack the putative binding motif reported in this study (see below).

A putative DR1 binding motif based on the sequence alignments of the core epitopes (the minimum length) of certain naturally processed peptides is shown in Table 3. The peptides listed in this table include those determined

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herein for HLA-DR1, as well as a number of peptides identified by others and known to bind DR1 (reference #6 in this table being O'Sullivan et al., J. Immunol. 145:1799-1808, 1990; reference #17, Roche & Cresswell, J. Immunol. 144:1849-1856, 1990; reference #25, Guttinger et al., Intern. Immunol. 3:899-906, 1991; reference #27, Guttinger et al. EMBO J. 7:2555-2558, 1988; and reference #28, Harris et al., J. Immunol. 148:2169-2174, 1992). The key residues proposed in the motif are as follows: a positively charged group is located at the first position, referred to here as the index position for orientation (I); a hydrogen bond donor is located at I+5; and a hydrophobic residue is at I+9. In addition, a hydrophobic residue is often found at I+1 and/or I-1. Every naturally processed peptide sequenced from DR1 conforms to this motif (with the exception of the HLA-A2 peptide 103-116 (SEQ ID NO: 3) that lacks residue I+9). Because the putative motif is not placed in a defined position with respect to the first amino acid and because of the irregular length of bound peptides, it is impossible to deduce a motif from sequencing of peptide pools, as was done for class I molecules (Falk et al., Nature 351:290-296 (1991)). The Ii 96-110 peptide (SEQ ID NO: 25), a negative control peptide used in binding experiments, has the I and I+5 motif residues within its sequence, but is missing eight additional amino acids found in Ii 105-118 (SEQ ID NO: 16) (Table 3C).

A sequence comparison of 35 previously described DR1-binding synthetic peptides (O'Sullivan et al., J. Immunol. 145:1799-1808 (1990); Guttinger et al., Intern. Immunol. 3:899-906 (1991); Hill et al., J. Immunol. 147:189-197 (1991); Guttinger et al., EMBO J. 7:2555-2558 (1988); Harris et al., J. Immunol. 148:2169-2174 (1992)) also supports this motif. Of the 35 synthetic peptides, 21 (60%) have the precise motif, nine (30%) contain a single

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shift at either I or I+9, and the remaining five (10%) have a single substitution at I (Table 3B and C). Interestingly, in the latter peptides, a positive charge at I is always replaced by a large hydrophobic residue (Table 8C); a pocket has been described in class I molecules that can accommodate this precise substitution (Latron et al., Proc. Natl. Acad. Sci. USA 88:11325-11329 (1991)). Contributions by the other eight amino acids within the motif or the length of the peptide have not been fully evaluated and may compensate for shifted/missing residues in those peptides exhibiting binding. Evaluation of the remaining 117 non-DR1 binding peptides cited in those studies (which peptides are not included in Table 3) indicates that 99 (85%) of these peptides do not contain the DR1 motif proposed herein. Of the remaining 18 peptides (15%) that do not bind to DR1 but which do contain the motif, 6 (5%) are known to bind to other DR allotypes; the remaining 12 peptides may have unfavorable interactions at other positions which interfere with binding.

In contrast to the precise N-terminal cleavages observed in the previous study of six peptides bound to the mouse class II antigen termed I-A<sup>b</sup> and five bound to mouse I-E<sup>b</sup> (Rudensky et al., Nature 356:622-627 (1991)), the peptides bound to DR1 are heterogeneous at both the N- and C-termini. In contrast to peptides bound to class I molecules, which are predominantly nonamers (Van Bleek and Nathenson, Nature 348:213-216 (1990); Rotzschke et al., Nature 348:252-254 (1990); Jardetzky et al., Nature 353:326-329 (1991); Hunt et al., Science 255:1261-1263 (1992)), class II peptides are larger and display a high degree of heterogeneity both in length and the site of terminal truncation, implying that the mechanisms of processing for class I and class II peptides are substantially different. Furthermore, the present results suggest that class II processing is a stochastic event and

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that a DR allotype may bind peptides of different lengths from a complex random mixture. The heterogeneity observed may be solely due to protection of bound peptides from further degradation. Thus, class II molecules would play an active role in antigen processing (as previously proposed (Donermeyer and Allen, J. Immunol. 142:1063-1068 (1989)) by protecting the bound peptides from complete degradation. Alternatively, the predominance of 15mers bound to DR1 (as detected by both the MALD-MS and the yields of sequenced peptides) could be the result of trimming of bound peptides. In any event, the absence of detectable amounts of peptides shorter than 13 and longer than 25 residues suggests that there are length constraints intrinsic either to the mechanism of peptide binding or to antigen processing. The predominance of peptides bound to DR1 that are derived from endogenously synthesized proteins, and particularly MHC-related proteins, may result from the evolution of a mechanism for presentation of self peptides in connection with the generation of self tolerance.

## II. Other HLA-DR molecules.

The sequences of naturally processed peptides eluted from each of DR2, DR3, DR4, DR7 and DR8 are shown in Tables 4-8, respectively. In addition to those peptides shown in Table 4, it has been found that DR2 binds to long fragments of HLA-DR2a  $\beta$ -chain and HLA-DR2b  $\beta$ -chain, corresponding to residues 1-126 or 127 of each of those proteins. Presumably, only a short segment of those long fragments is actually bound within the groove of DR2, with the remainder of each fragment protruding from one or both ends of the groove. Table 9 gives sequences of DR1 from another cell line which does not have wild-type Ar, but which has bound A2-like peptides. Table 10 gives sequences of peptides eluted from DR4 and DR11 molecules expressed in

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cells from a human spleen. These data demonstrate the great prevalence of self peptides bound, compared to exogenous peptides. The data also show that the A2 and Ii peptides occur repeatedly. In addition, certain of the  
5 Tables include peptides that appear to derive from viral proteins, such as Epstein-Barr virus major capsid protein, which are likely to be present in the cells studied.

### III. Peptide Delivery

#### Genetic Constructions.

10 In order to prepare genetic constructs for in vivo administration of genes encoding immunomodulatory peptides of the invention, the following procedure is carried out.

Overlapping synthetic oligonucleotides were used to generate the leader peptide/blocking peptide mini-genes  
15 illustrated in Fig. 3 by PCR amplification from human HLA-DR $\alpha$  and invariant chain cDNA templates. These mini-genes encode the Ii peptide fragments KMRMATPLLMQALPM (or Ii<sub>15</sub>; SEQ ID NO: 15) and LPKPPKPVSKMRMATPLLMQALPM (or Ii<sub>24</sub>; SEQ ID NO: 7). The resulting constructs were cloned into pGEM-2  
20 (Promega Corp.) to form the plasmids pGEM-2- $\alpha$ -Ii<sub>15</sub> and pGEM-2- $\alpha$ -Ii<sub>24</sub>, with an upstream T7 promoter for use in the in vitro transcription/translation system described below.

For in vivo expression, each mini-gene was subsequently subcloned from the pGEM-2 derivatives into a  
25 transfection vector, pH $\beta$ actin-1-neo (Gunning et al., (1987) Proc. Natl. Acad. Sci. U.S.A. 84:4831), to form the plasmids pH $\beta$ actin- $\alpha$ -Ii<sub>15</sub> and pH $\beta$ actin- $\alpha$ -Ii<sub>24</sub>. The inserted mini-genes are thus expressed in vivo from the constitutive/strong human  $\beta$  actin promoter. In addition,  
30 the mini-genes were subcloned from the pGEM-2 derivatives into the vaccinia virus recombination vector pSC11 (S. Chakrabarti et al. (1985) Mol. Cell. Biol. 5, 3403-3409) to form the plasmids pSC11- $\alpha$ -Ii<sub>15</sub> and pSC11- $\alpha$ -Ii<sub>24</sub>. Following

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recombination into the viral genome the inserted mini-genes are expressed from the strong vaccinia p<sub>7.5</sub> promoter.

Intracellular trafficking signals added to peptides.

Short amino acid sequences can act as signals to target proteins to specific intracellular compartments. For example, hydrophobic signal peptides are found at the amino terminus of proteins destined for the ER, while the sequence KFERQ (SEQ ID NO: 153) (and other closely related sequences) is known to target intracellular polypeptides to lysosomes, while other sequences target polypeptides to endosomes. In addition, the peptide sequence KDEL (SEQ ID NO: 152) has been shown to act as a retention signal for the ER. Each of these signal peptides, or a combination thereof, can be used to traffic the immunomodulating peptides of the invention as desired. For example, a construct encoding a given immunomodulating peptide linked to an ER-targeting signal peptide would direct the peptide to the ER, where it would bind to the class II molecule as it is assembled, preventing the binding of intact Ii which is essential for trafficking. Alternatively, a construct can be made in which an ER retention signal on the peptide would help prevent the class II molecule from ever leaving the ER. If instead a peptide of the invention is targeted to the endosomic compartment, this would ensure that large quantities of the peptide are present when invariant chain is replaced by processed peptides, thereby increasing the likelihood that the peptide incorporated into the class II complex is the high-affinity peptides of the invention rather than naturally-occurring, potentially immunogenic peptides. The likelihood of peptides of the invention being available incorporation into class II can be increased by linking the peptides to an intact Ii polypeptide sequence. Since Ii is known to traffic class II molecules to the endosomes, the hybrid Ii would

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carry one or more copies of the peptide of the invention along with the class II molecule; once in the endosome, the hybrid II would be degraded by normal endosomal processes to yield both multiple copies of the peptide of the invention or molecules similar to it, and an open class II binding cleft. DNAs encoding immunomodulatory peptides containing targeting signals will be generated by PCR or other standard genetic engineering or synthetic techniques, and the ability of these peptides to associate with DR molecules will be analyzed in vitro and in vivo, as described below.

It is proposed that the invariant chain prevents class II molecules from binding peptides in the ER and may contribute to heterodimer formation. Any mechanism that prevents this association would increase the effectiveness of class II blockade. Therefore, a peptide corresponding to the site on Ii which binds to the class II heterodimer, or corresponding to the site on either the  $\alpha$  or  $\beta$  subunit of the heterodimer which binds to Ii, could be used to prevent this association and thereby disrupt MHC class II function.

#### In Vitro Assembly.

Cell free extracts are used routinely for expressing eukaryotic proteins (Krieg, P. & Melton, D. (1984) Nucl. Acids Res. 12, 7057; Pelham, H. and Jackson, R. (1976) Eur. J. Biochem. 67, 247). Specific mRNAs are transcribed from DNA vectors containing viral RNA polymerase promoters (Melton, D. et al. (1984) Nucl. Acids Res. 12, 7035), and added to micrococcal nuclease-treated cell extracts. The addition of  $^{35}\text{S}$  methionine and amino acids initiates translation of the exogenous mRNA, resulting in labeled protein. Proteins may be subsequently analyzed by SDS-PAGE and detected by autoradiography. Processing events such as signal peptide cleavage and core glycosylation are



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initiated by the addition of microsomal vesicles during translation (Walter, P. and Blobel, G. (1983), Meth. Enzymol., 96, 50), and these events are monitored by the altered mobility of the proteins in SDS-PAGE gels.

5       The ability of peptides containing a signal peptide sequence to be accurately processed and to compete with invariant chain for class II binding in the ER are assayed in the in vitro system described above. Specifically, DR1  $\alpha$ - and  $\beta$ -chain and invariant chain peptide constructs  
10 described above are transcribed into mRNAs, which will be translated in the presence of mammalian microsomal membranes. Association of the DR heterodimer with Ii is determined by immunoprecipitation with antisera to DR and Ii. Addition of mRNA encoding the peptide of the invention  
15 to the translation reaction should result in a decreased level of coimmunoprecipitated Ii, and the concomitant appearance of coimmunoprecipitated peptide, as determined by SDS-PAGE on TRIS-Tricine gels. These experiments will provide a rapid assay system for determining the potential  
20 usefulness of a given blocking peptide as a competitor for Ii chain binding in the ER. Those peptides of the invention which prove to be capable of competing successfully with Ii in this cell-free assay can then be tested in intact cells, as described below.

#### 25 In Vivo Assembly.

Human EBV-transformed B cell lines LG-2 and HOM-2 (homozygous for HLA-DR1) and the mouse B cell hybridoma LK35.2 are transfected with either 50 $\mu$ g of linearized pH $\beta$ actin- $\alpha$ -Ii<sub>15</sub> or pH $\beta$ actin- $\alpha$ -Ii<sub>24</sub> or (as a control)  
30 pH $\beta$ actin-1-neo by electroporation (150mV, 960 $\mu$ F, 0.2cm cuvette gap). Following electroporation, the cells are cultured in G418-free medium until total recovery (approximately 4 days). Each population is then placed under G418 selection until neomycin-expressing resistant

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populations of transfectants are obtained (approximately 1-2 months). The resistant populations are subcloned by limiting dilution and the clonality of stable transfectants determined by PCR amplification of blocking peptide mRNA expression.

Stable transfectants of LG-2 and HOM-2 carrying blocking peptide mini-genes or negative control vectors are grown in large-scale culture conditions until 20 grams of pelleted cell mass is obtained. The HLA-DR expressed by each transfectant is purified, and the bound peptide repertoire (both from within the cell and from the cell surface) analyzed as described above. Successful demonstration of a reduction in the total bound peptide diversity will be conclusive evidence of intracellular delivery of immuno-modulatory peptides.

A second cell-based assay utilizes stable transfectants of LK35.2 cells carrying blocking peptide mini-genes or negative control vectors; these cells are used as APCs in T cell proliferation assays. Each transfectant is cultured for 24 hours in the presence of different dilutions of hen egg lysozyme (HEL) and HEL-specific T cell hybridomas. The relative activation of the T cells present in each assay (as measured by lymphokine production) is determined using the publicly available lymphokine dependent cell line CTLL2 in a <sup>3</sup>H-thymidine incorporation assay (Vignali et al. (1992) J.E.M. 175:925-932). Successful demonstration of a reduction in the ability of blocking peptide expressing transfectants to present HEL to specific T cell hybridomas will be conclusive evidence of intracellular delivery of immuno-modulatory peptides. Cells of the human TK<sup>-</sup> cell line 143 (ATCC) are infected with vaccinia virus (strain WR, TK<sup>+</sup>) (ATCC), and two hours postinfection, pSC11- $\alpha$ -Ii<sub>15</sub> or pSC11- $\alpha$ -Ii<sub>24</sub> or pSC11 is introduced into the infected cells by calcium phosphate precipitation. TK<sup>-</sup> recombinants are

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selected for with br modeoxyuridin at 25 $\mu$ g/ml. Recombinant plaques are screened by PCR for the presence of mini-gene DNA. Recombinant virus is cloned by three rounds of limiting dilution to generate pure clonal viral stocks.

5 In experiments analogous to the transfection experiments described above, recombinant vaccinia viruses encoding mini-genes or vector alone will be used to infect large-scale cultures of the human EBV transformed B cell lines LG-2 and HOM-2. Following infection, the HLA-DR is  
10 purified and the bound peptide repertoire analyzed as described above. A reduction of the complexity of the bound peptide population and a significant increase in the relative amount of Ii peptides bound are conclusive evidence that vaccinia can deliver blocking peptides to  
15 human APCs.

The same recombinant vaccinia viruses encoding mini-genes or vector will be used to infect mice experiencing experimentally-induced autoimmunity. A number of such models are known and are referred in Kronenberg, Cell  
20 65:537-542 (1991).

#### Liposomal Delivery of Synthetic Peptides or Mini-gene Constructs.

Liposomes have been successfully used as drug carriers and more recently in safe and potent adjuvant  
25 strategies for malaria vaccination in humans (Fries et al. (1992), Proc. Natl. Acad. Sci. USA 89:358). Encapsulated liposomes have been shown to incorporate soluble proteins and deliver these antigens to cells for both in vitro and  
30 in vivo CD8<sup>+</sup> mediated CTL response (Reddy et al., J. Immunol. 148:1585-1589, 1992; and Collins et al., J. Immunol. 148:3336-3341, 1992). Thus, liposomes may be used as a vehicle for delivering synthetic peptides into APCs.

Harding et al. (Cell (1991) 64, 393-401) have demonstrated that the targeting of liposome-delivered

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antigen to either of two intracellular class II-loading compartments, early endosomes and/or lysosomes, can be accomplished by varying the membrane composition of the liposome: acid-sensitive liposomes were found to target  
5 their contents to early endosomes, while acid-resistant liposomes were found to deliver their contents to lysosomes. Thus, the peptides of the invention will be incorporated into acid-sensitive liposomes where delivery to endosomes is desired, and into acid-resistant liposomes  
10 for delivery to lysosomes.

Liposomes are prepared by standard detergent dialysis or dehydration-rehydration methods. For acid-sensitive liposomes, dioleoylphosphatidylethanolamine (DOPE) and palmitoylhomocystein (PHC) are utilized, while  
15 dioleoylphosphatidylcholine (DOPC) and dioleoylphosphatidylserine (DOPS) are used for the preparation of acid-resistant liposomes.  $10^{-5}$  mol of total lipid (DOPC/DOPS or DOPE/PHC at 4:1 mol ratios) are dried, hydrated in 0.2 ml of HEPES buffered saline (HBS) (150 mM  
20 NaCl, 1 mM EGTA, 10mM HEPES pH 7.4) and sonicated. The lipid suspensions are solubilized by the addition of 0.1 ml of 1 M octylglucoside in HBS. The peptides to be entrapped are added to 0.2 ml of 0.6 mM peptide in 20% HBS. The mixture is then frozen, lyophilized overnight, and  
25 rehydrated. These liposomes will be treated with chymotrypsin to digest any surface-bound peptide. Liposome delivery to EBV-transformed cell lines (as described above) will be accomplished by 12-16 hour incubation at 37°C. HLA-DR will be purified from the liposome treated cells and  
30 bound peptide analyzed as above.

Alternatively, the liposomes are formulated with the DNA mini-gene constructs of the invention, and used to deliver the constructs into APCs either in vitro or in vivo.

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Human immunization will be carried out under the protocol approved by both The Johns Hopkins University Joint Committee for Clinical Investigation and the Human Subject Research Review Board of the Office of the Surgeon  
5 General of the U.S. Army (Fries et al. (1992), Proc. Natl. Acad. Sci. U.S.A. 89:358-362), using dosages described therein, or other dosages described in the literature for liposome-based delivery of therapeutic agents.

Delivery via Immune-stimulating Complexes (ISCOMS).

10 ISCOMS are negatively charged cage-like structures of 30-40nm in size formed spontaneously on mixing cholesterol and Quil A (saponin). Protective immunity has been generated in a variety of experimental models of  
15 induced tumors, using ISCOMS as the delivery vehicle for antigens (Mowat and Donachie) Immunology Today 12:383-385, 1991. Doses of antigen as low as 1 $\mu$ g encapsulated in ISCOMS have been found to produce class I mediated CTL  
20 responses, where either purified intact HIV-1-IIIB gp 160 envelope glycoprotein or influenza hemagglutinin is the antigen (Takahashi et al., Nature 344:873-875, 1990). Peptides are delivered into tissue culture cells using ISCOMS in a manner and dosage similar to that described  
25 above for liposomes; the class II peptide binding of delivered peptides are then determined by extraction and characterization as described above. ISCOM-delivered peptides of the invention which are effectively utilized by cultured cells are then tested in animals or humans.

In addition to delivery of the therapeutic synthetic  
30 peptides, ISCOMS could be constituted to deliver the mini-gene constructs to APCs, and thus serve as an alternative to the above-outlined vaccinia strategy.

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Immunogenic Peptide Delivery (Vaccines).

In addition to using the above-described intracellular delivery systems to deliver nonimmunogenic self peptides with the specific aim of down-modulating the immune system (thus alleviating autoimmune conditions), the delivery systems of the invention may alternatively be used as a novel means of vaccination, in order to stimulate a portion of the immune system of an animal. In the latter context, the delivery system is employed to deliver, into appropriate cells, DNA constructs which express immunogenic, pathogen-derived peptides intended to stimulate an immune response against a specific pathogen. Because the antigenic peptide is produced inside the target cell itself, the vaccine method of the invention ensures that there is no circulating free antigen available to stimulate antibody formation and thereby induce potentially deleterious or inappropriate immunological reactions. The immune response stimulated by vaccines of the invention is, because the vaccines are targeted solely to APC's, limited to the T cell mediated response, in contrast to standard vaccine protocols which result in a more generalized immune response. Although some of the peptide-presenting APC's will initially be lysed by host T cells, such lysis will be limited because, inter alia, the virus-based vaccine is non-replicative, i.e., each carrier virus can infect only one cell.

The model antigen that will be used to perfect and test the system of the invention is hen egg lysozyme (HEL). It is arguably the most well characterized protein for antigen presentation studies, to which there are numerous monoclonal antibodies and class I- and class II-restricted mouse T cell clones and hybridomas. The primary epitopes that will be studied are the peptide HEL 34-45, as both monoclonal antibodies and CD4+ T cell hybridomas are available, and peptide HEL 46-61, as both class I and class

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II-restricted T cell clones and hybridomas have been raised and are publicly available. These two sequences are thus proven immunogenic epitopes. Initially, four constructs encoding different polypeptides are analyzed: (a) whole, secreted HEL, (B) HEL 34-45, (c) HEL 46-61, and (d) HEL 34-61. The last three include a signal sequence known to be cleaved in these cells, e.g., IA<sup>k</sup> (MPRSRALILGVLALT~~TT~~MSLCGG; SEQ ID NO: ), which would result in targeting to the ER. All constructs are then subcloned into pH $\beta$ Apr-1 neo. The methodology for making these constructs is similar to that outlined above. The constructs are introduced into appropriate APCs, e.g., LK35.2 cells, by means of a conventional eukaryotic transfection or one of the delivery vehicles discussed above (e.g., vaccinia, liposomes, or ISCOMS). LK35.2 cells, which possess the mouse MHC Class II restriction molecules IA<sup>k</sup> and IE<sup>k</sup>, transfected with each of the constructs are tested for their ability to stimulate the appropriate class I and class II-restricted T cell hybridomas and clones using standard techniques. Whether class I stimulation is observed will depend on whether peptide trimming can occur in the ER, in order to produce an 8-10-mer suitable for binding to class I molecules. If these constructs are ineffective for class I stimulation, they can be modified in order to produce a more effective peptide for class I binding. If these constructs prove to be less effective for class II-restricted responses, they can be tagged with endosomal and/or lysosomal targeting sequences as discussed in Section V.

The effectiveness of targeting signals used to direct immunogenic peptides to particular intracellular organelles would be monitored using electron microscopic analysis of immunogold stained sections of the various transfectants. Rabbit anti-peptide antisera would be produced and affinity purified for this application. In

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addition, monoclonal antibody HF10, which recognizes HEL 34-45, will be used.

Once a construct is defined that can be effectively presented by transfectants in vitro, its effectiveness in vivo will be determined. This can be tested by injection of the transfectants i.p. and/or s.c. into C3H/Balb/c F1 mice, or by injection of the construct incorporated into an appropriate delivery vehicle (e.g., liposome, ISCOMS, retrovirus, vaccinia). Optimal protocols and doses for such immunizing injections can be determined by one of ordinary skill in the art, given the disclosures provided herein. Efficiency of immunization can be tested by standard methods such as (a) proliferation of class II-restricted T cells in response to HEL pulsed APCs, (b) CTL response to <sup>51</sup>Cr-labeled targets, and (c) serum antibody titre as determined by ELISA.

Once the details of the vaccine delivery system of the invention are optimized, constructs encoding peptides with useful immunizing potential can be incorporated into the system. Such peptides can be identified by standard means now used to identify immunogenic epitopes on pathogen-derived proteins. For example, candidate peptides for immunization may be determined from antibody and T cell analysis of animals infected with a particular pathogen. In order to obtain a protective and effective anamnestic response, the peptides used for vaccination should ideally be those which are presented with the highest frequency and efficiency upon infection. This could best be determined by using the procedures outlined in the experimental section above to extract and characterize the peptides bound by MHC class II molecules from infected cells. Given allelic restriction of immunogenic peptides (in contrast to the observed degenerate binding of self peptides of invention), a mini-gene encoding several immunogenic peptides will probably be required to provide a vaccine



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useful for the entire population. Vaccine administration and dosage are as currently employed to smallpox vaccination.

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TABLE 1  
LG-2/HLA-DR1 BINDING PEPTIDES

PROTEIN SOURCE	POSITION	SEQUENCE	SEQ ID NO.	LENGTH	FRACTION	MW	MASS SPEC	YIELD
Pseudo HLA-A2	103-120	VGSDRFLRGYNATDG	1	18	DR1S-59	2190.4	2190.4	39.5
	103-117	VGSDRFLRGYNAT	2	15	DR1S-58	1855.0	1854.4	907.5
	103-116	VGSDRFLRGYNAT	3	14	DR1S-58	1784.0	1783.6	53.3
	104-117	GSDRFLRGYNAT	4	14	DR1S-56	1755.3	1755.2	96.5
	105-117	SDRFLRGYNAT	5	13	DR1S-56	1698.2	1698.8	<u>48.8</u>
Invariant Chain (11)	97-121	LPKPKPVSKRMATPLLMOALPHG	6	25	DR1S-88	2733.5	2734.5	40.5
	97-120	LPKPKPVSKRMATPLLMOALPH	7	24	DR1S-88	2676.4	2675.9	80.8
	98-121	PKPKPVSKRMATPLLMOALPHG	8	24	DR1S-86	2620.2	2619.7	91.5
	97-119	LPKPKPVSKRMATPLLMOALP	9	23	DR1S-86	2545.2	2544.5	112.2
	98-120	PKPKPVSKRMATPLLMOALPH	10	23	DR1S-87	2563.2	2562.3	145.0
	99-120	KPKPVSKRMATPLLMOALPH	11	22	DR1S-87	2466.1	2465.8	101.5
	98-119	PKPKPVSKRMATPLLMOALP	12	22	DR1S-84	2432.0	2431.7	72.5
	99-119	KPKPVSKRMATPLLMOALP	13	21	DR1S-84	2334.9	2334.2	31.6
	100-119	PKPVSKRMATPLLMOALP	14	20	DR1S-86	2206.7	2207.4	89.8
	106-120	KRMATPLLMOALPH	15	15	DR1S-88	1732.2	1731.9	178.5
	106-119	KRMATPLLMOALP	16	14	DR1S-86	1601.0	1600.2	<u>162.0</u>
Na <sup>+</sup> /K <sup>+</sup> ATPase	199-216	IPADLR11SANGCKVDS	17	18	DR1S-56	1886.6	1885.8	48.8
Transferrin Recept.	680-696	RVEYHFLSPYSPKES	18	17	DR1S-58	2035.3	2036.8	30.3
Bovine Fetuin	56-74	YKTLNQIDSKVAPRRPT	19	19	DR1S-51	2237.6	2236.5	<u>69.0</u>
	56-73	YKTLNQIDSKVAPRRP	20	18	DR1S-50	2338.7	2338.5	32.5
HLA-DR $\beta$ -chain	43-61	DVGEYRAVELGRDAEYV	21	19	DR1S-51	2226.5	7	
Carboxypeptidase E	101-115	EPGEPEFYIGNHG	22	15	DR1S-48	1704.9	1700.4*	ESI-MS

TABLE 2  
PEPTIDE BINDING TO HLA-DR1

PEPTIDE <sup>a</sup>	SEQ ID NO.	LENGTH	K <sub>i</sub> vs HA 307-319 <sup>b</sup> nM	SDS-Resistance <sup>c</sup> nM
HLA-A2 103-117	2	15	49 ± 3	+
II 105-119	15	15	< 10	+
II 97-120	7	24	33 ± 5	+
Me+/K+ ATPase 199-216	17	18	68 ± 9	+
Transf. Recept. 680-696	18	17	< 10	+
Bovine Fetuin 56-72	23	19	66 ± 18	+
HA 307-319	24	14	< 10	+
II 97-111	25	15	> 10 <sup>4</sup>	-
β <sub>2</sub> m 52-64	26	13	> 10 <sup>4</sup>	-

<sup>a</sup> The first six entries correspond to peptides found associated with HLA-DR1 and the sequences are shown in Table 1. Two control peptides were also tested: β<sub>2</sub>m 52-64, SDSLSTQWSFLL, is from human β<sub>2</sub>-microglobulin and II 96-110, LPKPPKPVSKRMAT is a truncated version of the longest invariant chain derived peptide isolated from HLA-DR1. Peptides were synthesized using solid-phase Fmoc chemistry, deprotected and cleaved using standard methods, then purified by RPC. Purified peptides were analyzed by mass spectrometry and concentrations were determined by quantitative ninhydrin analysis.

<sup>b</sup> Inhibition constants (K<sub>i</sub>) were measured as the concentration of test peptide which inhibited 50% of the <sup>125</sup>I-labeled HA 307-319 binding to "empty" HLA-DR1 produced in Sf9 insect cells (20). HA 307-319 was labeled using Me<sup>125</sup>I and chloramine-T and isolated by gel filtration. Specific activity, determined by BCA assay (Pierce) and gamma counting, was 26,000 cpm/pmol. 10 nM labeled peptide and 10 nM purified HLA-DR1 were mixed with 10 different concentrations (10 nM to 10 μM) of synthetic cold competitor peptide in phosphate-buffered saline, pH 7.2, containing 1 mM EDTA, 1 mM PMSF, 0.1 mM iodoacetamide, and 3 mM NaH<sub>2</sub>PO<sub>4</sub>, and incubated at 37°C for 85 hours. Free and bound peptide were separated by native gel electrophoresis (33) and bound radioactivity was quantitated using a Fujix imaging plate analyzer (BAS 2000) after four hour exposures on the phosphor-imaging plates. Percent inhibition was calculated as the ratio of background-corrected radioactivity in the sample to background-corrected radioactivity in a parallel sample containing no competitor peptide. Under these conditions, K<sub>i</sub> measurements < 10 nM could not be accurately determined.

<sup>c</sup> The ability of the synthetic peptides to confer resistance to SDS-induced chain dissociation of HLA-DR1 produced in insect cells was determined as described (20). Briefly, 20 μM HLA-DR1 was incubated with five-fold excess of synthetic peptide at 37°C for 85 hours, in phosphate-buffered saline (pH 7.2) with the protease inhibitor mixture described above. After incubation, the samples were analyzed by SDS-PAGE with and without boiling prior to loading. Peptides which prevented SDS-induced chain dissociation are indicated positive (+) and those that did not negative (-).

TABLE 3 - PUTATIVE HLA-DR1 PEPTIDE BINDING MOTIF

A PROTEIN SOURCE	PEPTIDE SEQUENCE	SEQ ID NO.	LENGTH	POSITION	REFERENCE
HLA-A2	SDVFLRCYHOYA	5	13	105-117	This study
Invariant Chain	KRMNAIPLIQALP	16	14	105-118	
Na+/K+ ATPase	IPADLRITISANGCYDMS	17	18	199-216	
Transferrin Receptor	RVEYHFLSPYSPKESP	18	17	680-696	
Bovine Fetuin	YKNTLHQIDSVCVAPRRP	20	18	56-73	
B HEL	KYFGRCLEAAAKRHGLD	27	18	1-18	
	RNRCKGTDVQALIRGCRIL	28	18	112-129	
$\beta_2^m$	HPPHIEIOMLKNGKKI	29	16	31-46	
PLA2	HELGRFHTDAGCRTH	30	16	19-34	
	SEPKVYQVDFLRKY	31	14	115-128	
NASE	ATSTKLNKEPATILKAIDG	32	20	1-20	
	PATLIKAIDGQIVKLYKGO	33	20	11-30	
	DRVKLWYGGPHIFRLLLVD	34	20	21-40	
	VAYVYKPNHTHEOHLKSEA	35	20	111-130	
HIV p13	QGGEPIDKELYPLTSL	36	16	97-112	
HIV p17	GARASVLSGGELOKME	37	16	1-16	
Influenza HA	RTLYQNVGTIVSVGTSTLNK	38	20	187-206	
Influenza HA	PKYVKQHTLKLAT	24	13	307-319	
P. falcip. p190	LKSLVFGIRKPLDHI	39	15	249-263	
P. falcip. Cs	RHIEGTLKKIKHS	40	13	329-341	
Chicken OVA	DVFEKLSVNHAEHET	41	16	15-30	
DR1 $\beta$ chain	GDTSPRTLYGKKECHFFNG	42	20	1-20	
	TERVALLERCITYMQEESVRFDS	43	22	21-42	
	DLLEORRAAVDITYCRHNYGVGESFT	44	25	66-90	
p Cyt c	KAERAQLIATLKQATAK	45	17	88-104	
Myelin basic prot.	GRTOOEIPVYVYFFQNIIVTRTPPP	46	24	75-98	

Table 3, continued

A	PROTEIN SOURCE	PEPTIDE SEQUENCE	SEQ ID NO.	LENGTH	POSITION	REFERENCE
C	Influenza Matrix	PLKAEIAQRLEDV	47	13	19-31	6
	HIV p17	GGILGQLOPQSLQGCSE	48	16	57-72	6
	$\beta_2^m$	IQVTSRHPPEKPKHI	49	16	7-22	6
	PLA <sub>2</sub>	INTKCYKLEHPVIGCG	50	16	85-100	6
	P. falcip. p190	IKLNIYFDLIRAKL	51	14	211-224	25
		IDTLKKNEIKEL	52	13	338-350	25
	DR1 $\beta$ chain	DVGEIRAVTELGRDPAETIM	53	20	43-62	28
	HIV p17	ERFAVNPGLLETSECC	54	16	41-56	6
	HEL	DNYRGYSLOHNVCLAKYFSNFTQ	55	23	20-42	6
	WASE	EALVRQGLAKVAIVYKPKNT	56	20	101-120	6
	HIV p25	PIVQNLQGMVYQDAIS	57	16	1-16	6
		SALSEGATPODLNTHL	58	16	41-56	6
	$\beta_2^m$	SFTLANIEFTPTETD	59	16	61-76	6
	PLA <sub>2</sub>	KMYFNLINTKCYKLEH	60	16	79-94	6

TABLE 4  
HST/HLA-DR2 BINDING PEPTIDES

PROTEIN SOURCE	POSITION	SEQUENCE	SEQ ID NO.	LENGTH	FRACTION	MW	MASS SPEC
Pseudo HLA-A2	103-120	VGSDARFLRGTHQYADG	1	18	DR2-3-57	2190.4	2189.0
	103-119	VGSDARFLRGTHQYAD	61	17	DR2-3-57	2133.3	2131.8
	104-119	GSDARFLRGTHQYAD	62	16	DR2-3-56	2034.3	2040.4
	103-117	VGSDARFLRGTHQYA	2	15	DR2-3-56	1855.0	1858.5
	103-116	VGSDARFLRGTHQY	3	14	DR2-3-56	1784.0	1786.3
	104-117	GSDARFLRGTHQYA	4	14	DR2-3-55	1755.3	1755.0*
	105-117	SDARFLRGTHQYA	5	13	DR2-3-56	1698.2	1702.6
	97-120	LPDPPKPVSDRRNATPLLMQALPM	7	24	DR2-3-70	2676.4	2675.0*
	98-120	PKDPPKPVSDRRNATPLLMQALPM	10	23	DR2-3-70	2563.2	2562.0*
	99-120	KPKPKPVSDRRNATPLLMQALPM	11	22	DR2-3-70	2466.1	2465.0*
Invariant Chain (Ii)	98-119	PKDPPKPVSDRRNATPLLMQALP	12	22	DR2-3-66	2432.0	2437.0
	99-119	KPKPKPVSDRRNATPLLMQALP	13	21	DR2-3-66	2334.9	2340.0
	100-119	PKPKPVSDRRNATPLLMQALP	63	20	DR2-3-70	2206.7	2207.0*
	106-124	KRMATPLLMQALPMQALP	64	19	DR2-3-71	2070.5	2074.3
	106-120	KRMATPLLMQALPM	15	15	DR2-3-70	1732.2	1732.0*
	97-119	NIVIKESHSSTAAATHEVPEVTFS	158	23	DR2-3-44	2476.8	2478.1
	97-112	NIVIKESHSSTAAATHEV	159	16	DR2-3-41	1716.9	1717.0
	42-59	SDGVYTRAVTPGCRPOAE	160	18	DR2-3-41	1917.1	1920.5
	43-59	DVGVTYTRAVTPGCRPOAE	161	17	DR2-3-41	1850.0	1833.3
	43-57	DVGVTYTRAVTPGCRPD	162	15	DR2-3-41	1629.8	1632.9
HLA-DR $\alpha$ -chain	182-194	APSPLPETTERNVV	163	13	DR2-3-36	1353.5	1362.0
	182-198	APSPLPETTERNVVYCALG	164	17	DF2-3-41	1697.9	1701.0
	59-81	ENHIFLGATWYIVLNEEDLQKV	65	23	DR2-3-65	2746.1	2746.6
(RET) Kinase-related transforming protein							
Guanylate-bind. Mannose-bind. prot.	434-450	QELDKKTYGVPRKIGIA	66	17	DR2-3-71	2063.4	2074.3
	174-193	IQMLIKEAFILGIDTEKTEG	67	20	DR2-3-70	2248.5	2248.0*



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TABLE 5  
WT-20/HLA-DR3 NATURALLY PROCESSED PEPTIDES

Protein Source	Position	Sequence	SEQ ID NO.	Length	Fraction	MW	Mass Spec.
Pseudo HLA-A2	103-117	VGSDURFLGGYQYA	2	15	DR3-2-63	1855.0	1863.9
HLA-A30	28-7	VDOTQVRFSDAASQ...	171	7	DR3-2-55	7	7
HLA-DR $\alpha$ -chain	111-129	PPEVTVLTHSPVELREPV	172	19	DR3-2-55	2090.4	2093.3
	111-128	PPEVTVLTHSPVELREPV	173	18	DR3-2-55	1991.2	1989.8
HLA-DR $\beta$ -chain	1-7	GDTRPFEYISTECHFF	79	18	DR3-2-73	7	7
Acetylcholine recept.	289-304	VFLLLADKVPETSL	174	16	DR3-2-65	1745.1	1750.1
Glucose-transport	459-474	TFDEIASGFRGGASQ	175	16	DR3-2-55	1670.8	1672.6
Sodium channel prot.	364-397	YGYTSTDTFSMAFL	176	14	DR3-2-41	1720.8	1720.5
Invariant chain	97-119	LKPKKPVSIORRNATPLLMDALP	9	23	DR3-2-73	2545.2	2554.0
(11)	98-119	PKPPKPVSIORRNATPLLMDALP	12	22	DR3-2-73	2432.0	2441.4
	99-119	KPPKPVSIORRNATPLLMDALP	13	21	DR3-2-73	2334.9	2345.3
	131-149	ATKGMHTEDHVMHLLQNA	177	19	DR3-2-69	2173.4	2179.3
CD45	1071-1084	GVKKNNHDEKIE	178	14	DR3-2-41	1666.8	1667.0
ICAM-2	64-76	LWKILLDEQAMK	179	13	DR3-2-51/52	1598.9	1602.4
Interferon $\gamma$ -receptor	128-147	GPPKLDIRKEEKQIMIDIFN	180	21	DR3-2-77	2505.0	2510.3
	128-148	GPPKLDIRKEEKQIMIDIFNP	181	20	DR3-2-77	2407.8	2412.4
IP-30	38-59	SPQLALDFFGNGPPVYKTKGL	182	22	DR3-2-77	2505.0	2510.3
	38-57	SPQLALDFFGNGPPVYKTKG	183	20	DR3-2-77	2122.4	2124.2
Cytochrome-b5 reduc.	155-172	GKFAIRPKKSNPIIRTV	184	18	DR3-2-51/52	2040.4	2043.2
EBV membrane antigen GP220	592-606	TGHGARTSTEPTDY	185	15	DR3-2-41	1593.6	1592.7
EBV tegument protein membrane p140	1395-1407	KELKRYEKLLRG	186	13	DR3-2-51/52	1747.1	1749.8





TABLE 6  
PRIEST/HLA-DR4 NATURALLY PROCESSED PEPTIDES

PROTEIN SOURCE	POSITION	SEQUENCE	SEQ ID NO.	LENGTH	FRACTION	MW	MASS SPEC
Ig kappa chain C region (human)	188-208	KKKYACEVTHQGLSSPVTK	80	21	DR4-2-45	2299.6	2304.0
	188-207	KKKYACEVTHQGLSSPVTK	81	20	DR4-2-47	2212.5	2213.0
	189-206	HKYVACEVTHQGLSSPVTV	82	18	DR4-2-43	1955.5	1952.1
	188-204	KKKYACEVTHQGLSSP	83	17	DR4-2-45	1883.1	1882.8
	187-203	EKKKYACEVTHQGLSS	84	17	DR4-2-45	1915.1	1922.5
	188-203	KKKYACEVTHQGLSS	85	16	DR4-2-54	1787.0	1787.0
	189-204	HKYVACEVTHQGLSSP	86	16	DR4-2-47	1755.0	1767.8
	187-202	EKKKYACEVTHQGLS	87	16	DR4-2-43	1828.0	1822.8
	188-202	KKKYACEVTHQGLS	88	15	DR4-2-51	1699.9	1708.3
	189-203	HKYVACEVTHQGLSS	89	15	DR4-2-45	1657.8	1667.0
	187-200	EKKKYACEVTHQGL	90	14	DR4-2-51	1628.8	1632.6
HLA-DR $\alpha$ -chain HLA-A2	182-198	APSLPETTENVYVLCG	91	17	DR4-2-43	1697.9	1700
	28-50	VQDTQVRFDSDAASORNEPRAP	195	23	DR4-2-58	2638.6	2641.5
	28-48	VQDTQVRFDSDAASORNEPR	92	21	DR4-2-56	2470.6	2472.9
	28-47	VQDTQVRFDSDAASORNEP	93	20	DR4-2-59	2314.5	2319.3
	28-46	VQDTQVRFDSDAASORNE	94	19	DR4-2-54	2217.2	2218.7
	30-48	DTQVRFDSDAASORNEPR	95	19	DR4-2-55	2256.4	2263.2
	31-49	TQVRFDSDAASORNEPRA	96	19	DR4-2-56	2212.4	2211.5
	28-44	VQDTQVRFDSDAASOR	97	17	DR4-2-55	1957.0	1963.1
	31-47	TQVRFDSDAASORNEP	98	17	DR4-2-56	1985.1	1987.5
	31-45	TQVRFDSDAASORH	99	15	DR4-2-54	1758.9	1761.0
	31-42	TQVRFDSDAAS	100	12	DR4-2-54	1343.4	1343.3
	28-50	VQDTQVRFDSDAASPRGEPRAP	101	23	DR4-2-56	2533.7	2536.7
	31-52	TQVRFDSDAASPRGEPRAPW	102	22	DR4-2-54	2489.7	2491.5
	28-48	VQDTQVRFDSDAASPRGEPR	103	21	DR4-2-54	2365.5	2368.1
	28-47	VQDTQVRFDSDAASPRGEPR	104	20	DR4-2-56	2209.3	2211.5
	28-46	VQDTQVRFDSDAASPRGE	105	19	DR4-2-56	2112.2	2113.9
HLA-C							



TABLE 7  
MAMU/HLA-DR7 NATURALLY PROCESSED PEPTIDES

PROTEIN SOURCE	POSITION	SEQUENCE	SEQ ID NO.	LENGTH	FRACTION	MW	MASS SPEC
Pseudo HLA-A2	105-124	SDURFLRGTHYATGQYI	207	20	DR7-2-61	2553.8	2556.5
	103-120	VGSDURFLRGTHYATDG	1	18	DR7-2-63	2190.4	2194
	103-117	VGSDURFLRGTHYA	2	15	DR7-2-63	1855.0	1860
	104-117	GSDURFLRGTHYA	208	14	DR7-2-61	1755.9	1760.8
	104-116	GSDURFLRGTHY	209	13	DR7-2-61	1684.8	1687.6
	105-117	SDURFLRGTHYA	210	13	DR7-2-61	1698.9	1704.1
HLA-A29	234-253	RPAGDGTGFKUASVVPSCG	124	20	DR7-2-66	2087.3	2092
	234-249	RPAGDGTGFKUASVV	125	16	DR7-2-63	1717	1718
	237-258	GDTGFKUASVVPSCGRTY	126	22	DR7-2-66	2436	2440
	237-254	GDTGFKUASVVPSCGE	127	18	DR7-2-66	1892.3	1892
	239-252	GTGFKUASVVPSC	128	14	DR7-2-66	1462	1465
	239-253	GTGFKUASVVPSCG	129	15	DR7-2-66	1718	1721
	239-261	GTGFKUASVVPSCGRTYCHV	130	23	DR7-2-66	2603	2606
	83-99	RETQISKINTQTYRENI	211	17	DR7-2-35	2082.3	2086.1
	83-98	RETQISKINTQTYREN	212	16	DR7-2-35	1969.1	1971.1
	83-97	RETQISKINTQTYRE	213	15	DR7-2-35	1855.0	1857.3
	101-126	RSNYTPITNPPEVTVTNSPVELREP	214	26	DR7-2-35	2924.2	2926.9
	58-78	GALAMIAVDKANKLEINTKSH	131	21	DR7-2-66	2229.5	2221
HLA-B*44	182-200	APSPLETTEENVYCALGLTV	215	20	DR7-2-42	1912.2	1917.7
	179-7	SLOSPITVEMRAQSEASGSKLSGIGFVL	216	7	DR7-2-35	7	7
	318-338	VTQYLWATGKRCUSLSQAR	217	21	DR7-2-71	2441.7	2445.1
	318-334	VTQYLWATGKRCUSLS	218	17	DR7-2-71	1999.2	2001.9
antigen heavy chain LIF receptor	854-866	TSILCYKREVIK	219	13	DR7-2-35	1696.0	1700.8
	188-201	KHKVYACEVTMOGL	220	14	DR7-2-61	1612.9	1615.6
	188-200	KHKVYACEVTMOG	221	13	DR7-2-61	1498.7	1501.0
	98-119	PKPPKPSVDSORWATPLLWQALP	12	22	DR7-2-72	2432.0	2436.6
Invariant Chain (Ii)	99-119	KPPKPSVDSORWATPLLWQALP	13	21	DR7-2-72	2334.9	2339.7
	492-516	GDRYPTKTVSGNLVGCALAGMLTI	222	25	DR7-2-71	2567.1	2567.3

Table 7, continued

PROTEIN SOURCE	POSITION	SEQUENCE	SEQ ID NO.	LENGTH	FRACTION	PM	MASS SPEC
Heat shock cognate	38-54	TPSVVAFDTQTERLIGDA	132	17	DR7-2-69	1856.0	1856.6
71 kD protein				17	DR7-2-72	1856.0	1857.0
Complement C9	38-52	TPSVVAFDTQTERLIG	133	15	DR7-2-69	1669.8	1671.9
Thromboxane-A	465-483	APVLISQKLSPIYNLVPVK	223	19	DR7-2-61	2079.5	2083.9
synthase	406-420	PAFRFTREAAQDCEV	224	15	DR7-2-71	1739.9	1743.0
EBV major capsid prot	1264-1282	VPGLYSPCRAFFNKEILL	225	18	DR7-2-54	2082.4	2081.2
	1264-1277	VPGLYSPCRAFFNK	226	14	DR7-2-54	1597.9	1598.6
Apolipoprotein B-100	1586-1608	KVDLTFKQHALLCSDYQADYES	227	23	DR7-2-54	2660.9	2662.5
	1586-1600	KVDLTFKQHALLC	228	15	DR7-2-54	1689.0	1687.7
	1942-1954	FSHDYRGSGTSHRL	229	13	DR7-2-42	1562.7	1567.5
	2077-2089	LPRYFEKIKRNTII	230	13	DR7-2-61	1650.0	1653.8

TABLE 8  
Z3.1/HLA-DQB NATURALLY PROCESSED PEPTIDES

PROTEIN SOURCE	POSITION	SEQUENCE	SEQ. ID NO.	LENGTH	FRACTION	MW	MASS SPEC
HLA-DR $\alpha$ -chain	158-180	SETVLPREDHLFRKFNLYLP	231	23	DRB-3-59	2889.3	2889.0
	182-198	APSPLPETENWYCALG	232	17	DRB-3-61	1697.9	1704.3
HLA-DR $\beta$ -chain	1-7	GDTRPRFLEYSTGEYFFNGITRV	233	7	DRB-3-75		
HLA-DP $\beta$ -chain	80-92	RHWELDEAVTLQ	234	13	DRB-3-76	1587.7	1591.3
LAM Blast-1 with N-acetylglucosamine	88-108	DPSGALYISKYKEDNSTYI	235	21	DRB-3-54	2543.6	2549.1
	92-108	GALYISKYKEDNSTYI	236	17	DRB-3-52	2116.1	2118.0
	129-146	DPVPKPVIKIEKIEDMOO	237	18	DRB-3-57	2081.4	2085.7
	129-143	DPVPKPVIKIEKIED	238	15	DRB-3-57	1720.0	1724.9
Ig kappa chain	63-80	FIFTISRLEPEDFAVYTC	239	18	DRB-3-57	2201.5	2203.6
	63-77	FIFTISRLEPEDFAV	240	15	DRB-3-57	1772.0	1777.0
LAR protein	1302-1316	DPVEMRLNHYQTPG	241	14	DRB-3-76	1675.9	1679.8
LIF receptor	709-726	YQLLRSHIGYIEELAPIV	242	18	DRB-3-66	2108.5	2112.0
IFN- $\alpha$ receptor	271-287	GMHLYKVKQIPDCENVK	243	17	DRB-3-66	2072.4	2075.1
Interleukin-8 receptor	169-188	LPFFLFRQAYNPNNSPVCY	244	20	DRB-3-59	2400.7	2402.5
Metalloproteinase inhibitor 2	187-214	OAKFFACIKRSDGSCAVYRGAAPPKQEF	245	28	DRB-2-63	3161.6	3164.9
Metalloproteinase inhibitor 1	187-205	OAKFFACIKRSDGSCAVYR	246	19	DRB-3-63	2235.5	2233.6
	101-118	NRSEEFLLAGKLDGGLLH	134	18	DRB-3-66	2040.3	2042.9
Cathepsin E	101-117	SEEFLLAGKLDGGLL	135	16	DRB-3-70	1789.0	1799.9
Cathepsin S	103-117	SEEFLLAGKLDGGLL	247	15	DRB-3-72	1632.9	1646.0
Cystatin SN	101-112	NRSEEFLLAGKL	248	12	DRB-3-66	1376.6	1381.8
Tubulin $\alpha$ -1 chain	89-112	GMFTVIPTGSSNLWPSVYCTSP	249	24	DRB-3-59	2662.9	2664.4
	189-205	YAFQYIIONKIGIDSDAS	68	17	DRB-3-63	1857.9	1857.1
	41-58	DEYRRLLYLRLAREGIV	250	18	DRB-3-63	2348.7	2348.0
	207-223	EATYDTCRRHLDIERPT	251	17	DRB-3-63	2077.3	2078.3
	207-219	EATYDTCRRHLDI	252	13	DRB-3-63	1593.8	1595.1
Myosin $\beta$ -heavy chain	1027-1047	MELEKIKKQVEQEKCEIQAL	253	21	DRB-3-59	2493.9	2494.0
Ca release channel	2614-2623	RPSKHLQHLR	254	10	DRB-3-68	1250.5	1254.8







TABLE 10  
SUMMARY OF NATURALLY PROCESSED PEPTIDES BOUND TO HLA-DR EXPRESSED IN NORMAL HUMAN SPLEEN

PROTEIN SOURCE	POSITION	SEQUENCE	SEQ ID NO.	LENGTH	MW	MASS SPEC
HLA-DR $\alpha$ -chain	71/133-156	SETVLPREDHLFRKFHYLPFLPS	140	24	2976	2982
	71/136-156	VFLPREDHLFRKFHYLPFLPS	141	21	2659	2666
	71/136-155	VFLPREDHLFRKFHYLPFLP	142	20	2572	2579
	71/136-151	VFLPREDHLFRKFHYL	143	16	2118	2126
Calgranulin B	33/25-33	KLGHPTLN	144	9	994	999
	42/88-116	WASKECHNEDEGPGCHNKTPGLCEGP	145	27	2915	2927
	43/88-116	WASKECHNEDEGPGCHNKTPGLCEGP	146	27	2017	2926
	42/104-121	GPDGRLLRCHNTOGK	188	16	2017	2023
Kinase C $\gamma$ chain (rat)	42/341-446	TLPPFQPIIDYGLD	70	16	1704	1705
HLA-DR4 $\beta$ chain	45/129-144	VRVFRNGEETGWS	71	16	1892	1894
						MALD-MS

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SEQUENCE LISTING

## (1) GENERAL INFORMATION:

## (i) APPLICANT:

Robert G. Urban  
Roman M. Chicz  
Dario A. A. Vignali  
Mary L. Hedley  
Lawrence J. Stern  
Jack L. Strominger

(ii) TITLE OF INVENTION: IMMUNOMODULATORY PEPTIDES

(iii) NUMBER OF SEQUENCES: 273

## (iv) CORRESPONDENCE ADDRESS:

(A) ADDRESSEE: Fish & Richardson  
(B) STREET: 225 Franklin Street  
(C) CITY: Boston  
(D) STATE: Massachusetts  
(E) COUNTRY: U.S.A.  
(F) ZIP: 02110-2804

## (v) COMPUTER READABLE FORM:

(A) MEDIUM TYPE: 3.5" Diskette, 1.44 Mb  
(B) COMPUTER: IBM PS/2 Model 50Z or 55SX  
(C) OPERATING SYSTEM: MS-DOS (Version 5.0)  
(D) SOFTWARE: WordPerfect (Version 5.1)

## (vi) CURRENT APPLICATION DATA:

(A) APPLICATION NUMBER:  
(B) FILING DATE:  
(C) CLASSIFICATION:

## (vii) PRIOR APPLICATION DATA:

(A) APPLICATION NUMBER: 07/925,460  
(B) FILING DATE: August 11, 1992

## (viii) ATTORNEY/AGENT INFORMATION:

(A) NAME: Clark, Paul T.  
(B) REGISTRATION NUMBER: 30,162  
(C) REFERENCE/DOCKET NUMBER: 00246/168001

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## (ix) TELECOMMUNICATION INFORMATION:

(A) TELEPHONE: (617) 542-5070  
(B) TELEFAX: (617) 542-8906  
(C) TELEX: 200154

## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 1:

## (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1:

Val Gly Ser Asp Trp Arg Phe Leu Arg Gly Tyr His Gln Tyr Ala Tyr  
1 5 10 15  
Asp Gly

## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 2:

## (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 15  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 2:

Val Gly Ser Asp Trp Arg Phe Leu Arg Gly Tyr His Gln Tyr Ala  
1 5 10 15

## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 3:

## (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 14  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 3:

Val Gly Ser Asp Trp Arg Phe Leu Arg Gly Tyr His Gln Tyr  
1 5 10

## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 4:

## (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1  
(B) TYPE: amino acid  
(C) STRANDEDNESS:

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(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 4:

Gly Ser Asp Trp Arg Phe Leu Arg Gly Tyr His Gln Tyr Ala  
 1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 5:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 13  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS:  
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 5:

Ser Asp Trp Arg Phe Leu Arg Gly Tyr His Gln Tyr Ala  
 1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 6:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 25  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS:  
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 6:

Leu Pro Lys Pro Pro Lys Pro Val Ser Lys Met Arg Met Ala Thr Pro  
 1 5 10 15

Leu Leu Met Gln Ala Leu Pro Met Gly  
 20 25

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 7:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 24  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS:  
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 7:

Leu Pro Lys Pro Pro Lys Pro Val Ser Lys Met Arg Met Ala Thr Pro  
 1 5 10 15

Leu Leu Met Gln Ala Leu Pro Met  
 20

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## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 8:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 24
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 8:

Pro Lys Pro Pro Lys Pro Val Ser Lys Met Arg Met Ala Thr Pro Leu  
1 5 10 15  
Leu Met Gln Ala Leu Pro Met Gly  
20

## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 9:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 23
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 9:

Leu Pro Lys Pro Pro Lys Pro Val Ser Lys Met Arg Met Ala Thr Pro  
1 5 10 15  
Leu Leu Met Gln Ala Leu Pro  
20

## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 10:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 23
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 10:

Pro Lys Pro Pro Lys Pro Val Ser Lys Met Arg Met Ala Thr Pro Leu  
1 5 10 15  
Leu Met Gln Ala Leu Pro Met  
20

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## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 11:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 22
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 11:

Lys Pro Pro Lys Pro Val Ser Lys Met Arg Met Ala Thr Pro Leu Leu  
1 5 10 15  
Met Gln Ala Leu Pro Met  
20

## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 12:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 22
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 12:

Pro Lys Pro Pro Lys Pro Val Ser Lys Met Arg Met Ala Thr Pro Leu  
1 5 10 15  
Leu Met Gln Ala Leu Pro  
20

## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 13:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 21
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 13:

Lys Pro Pro Lys Pro Val Ser Lys Met Arg Met Ala Thr Pro Leu Leu  
1 5 10 15  
Met Gln Ala Leu Pro  
20

## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 14:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20
- (B) TYPE: amino acid

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- (C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 14:

Pro Pro Lys Pro Val Ser Lys Met Arg Met Ala Thr Pro Leu Leu Met  
1 5 10 15  
Gln Ala Leu Pro  
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 15:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 15  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 15:

Lys Met Arg Met Ala Thr Pro Leu Leu Met Gln Ala Leu Pro Met  
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 16:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 14  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 16:

Lys Met Arg Met Ala Thr Pro Leu Leu Met Gln Ala Leu Pro  
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 17:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 18  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 17:

Ile Pro Ala Asp Leu Arg Ile Ile Ser Ala Asn Gly Cys Lys Val Asp  
1 5 10 15  
Asn Ser

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## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 18:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 17
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 18:

Arg Val Glu Tyr His Phe Leu Ser Pro Tyr Val Ser Pro Lys Glu Ser  
1 5 10 15  
Pro

## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 19:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 19
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 19:

Tyr Lys His Thr Leu Asn Gln Ile Asp Ser Val Lys Val Trp Pro Arg  
1 5 10 15  
Arg Pro Thr

## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 20:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 18
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 20:

Tyr Lys His Thr Leu Asn Gln Ile Asp Ser Val Lys Val Trp Pro Arg  
1 5 10 15  
Arg Pro

## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 21:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 19
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear



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(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 21:

Asp Val Gly Glu Tyr Arg Ala Val Thr Glu Leu Gly Arg Pro Asp Ala  
1 5 10 15  
Glu Tyr Trp

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 22:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 15  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 22:

Glu Pro Gly Glu Pro Glu Phe Lys Tyr Ile Gly Asn Met His Gly  
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 23:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 17  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 23:

Tyr Lys His Thr Leu Asn Gln Ile Asp Ser Val Lys Val Trp Pro Arg  
1 5 10 15  
Arg

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 24:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 13  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 24:

Pro Lys Tyr Val Lys Gln Asn Thr Leu Lys Leu Ala Thr  
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 25:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 15  
(B) TYPE: amino acid

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(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 25:

Leu Pro Lys Pro Pro Lys Pro Val Ser Lys Met Arg Met Ala Thr  
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 26:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 13  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 26:

Ser Asp Leu Ser Phe Ser Lys Asp Trp Ser Phe Tyr Leu  
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 27:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 27:

Lys Val Phe Gly Arg Cys Glu Leu Ala Ala Ala Met Lys Arg His Gly  
1 5 10 15

Leu Asp

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 28:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 28:

Arg Asn Arg Cys Lys Gly Thr Asp Val Gln Ala Trp Ile Arg Gly Cys  
1 5 10 15

Arg Leu

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 29:

(i) SEQUENCE CHARACTERISTICS:

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(A) LENGTH: 16  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS:  
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 29:

His Pro Pro His Ile Glu Ile Gln Met Leu Lys Asn Gly Lys Lys Ile  
 1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 30:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS:  
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 30:

Asn Glu Leu Gly Arg Phe Lys His Thr Asp Ala Cys Cys Arg Thr His  
 1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 31:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 14  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS:  
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 31:

Ser Lys Pro Lys Val Tyr Gln Trp Phe Asp Leu Arg Lys Tyr  
 1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 32:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS:  
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 32:

Ala Thr Ser Thr Lys Lys Leu His Lys Glu Pro Ala Thr Leu Ile Lys  
 1 5 10 15

Ala Ile Asp Gly  
 20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 33:

(i) SEQUENCE CHARACTERISTICS:

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(A) LENGTH: 20  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 33:

Pro Ala Thr Leu Ile Lys Ala Ile Asp Gly Asp Thr Val Lys Leu Met  
1 5 10 15  
Tyr Lys Gly Gln  
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 34:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 34:

Asp Arg Val Lys Leu Met Tyr Lys Gly Gln Pro Met Thr Phe Arg Leu  
1 5 10 15  
Leu Leu Val Asp  
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 35:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 35:

Val Ala Tyr Val Tyr Lys Pro Asn Asn Thr His Glu Gln His Leu Arg  
1 5 10 15  
Lys Ser Glu Ala  
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 36:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 36:

Gln Lys Gln Glu Pro Ile Asp Lys Glu Leu Tyr Pro Leu Thr Ser Leu  
 1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 37:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS:  
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 37:

Gly Ala Arg Ala Ser Val Leu Ser Gly Gly Glu Leu Asp Lys Trp Glu  
 1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 38:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS:  
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 38:

Arg Thr Leu Tyr Gln Asn Val Gly Thr Tyr Val Ser Val Gly Thr Ser  
 1 5 10 15  
 Thr Leu Asn Lys  
 20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 39:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 15  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS:  
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 39:

Leu Lys Lys Leu Val Phe Gly Tyr Arg Lys Pro Leu Asp Asn Ile  
 1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 40:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 13  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS:

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(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 40:

Lys His Ile Glu Gln Tyr Leu Lys Lys Ile Lys Asn Ser  
 1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 41:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS:  
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 41:

Asp Val Phe Lys Glu Leu Lys Val His His Ala Asn Glu Asn Ile Phe  
 1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 42:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS:  
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 42:

Gly Asp Thr Arg Pro Arg Phe Leu Trp Gln Leu Lys Phe Glu Cys His  
 1 5 10 15

Phe Phe Asn Gly  
 20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 43:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 22  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS:  
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 43:

Thr Glu Arg Val Arg Leu Leu Glu Arg Cys Ile Tyr Asn Gln Glu Glu  
 1 5 10 15

Ser Val Arg Phe Asp Ser  
 20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 44:

(i) SEQUENCE CHARACTERISTICS:

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- (A) LENGTH: 25
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 44:

Asp Leu Leu Glu Gln Arg Arg Ala Ala Val Asp Thr Tyr Cys Arg His  
 1 5 10 15  
 Asn Tyr Gly Val Gly Glu Ser Phe Thr  
 20 25

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 45:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 17
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 45:

Lys Ala Glu Arg Ala Asp Leu Ile Ala Tyr Leu Lys Gln Ala Thr Ala  
 1 5 10 15  
 Lys

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 46:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 24
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 46:

Gly Arg Thr Gln Asp Glu Asn Pro Val Val His Phe Phe Lys Asn Ile  
 1 5 10 15  
 Val Thr Pro Arg Thr Pro Pro Pro  
 20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 47:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 13
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 47:

Pro Leu Lys Ala Glu Ile Ala Gln Arg Leu Glu Asp Val  
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 48:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 48:

Arg Gln Ile Leu Gly Gln Leu Gln Pro Ser Leu Gln Thr Gly Ser Glu  
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 49:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 49:

Ile Gln Val Tyr Ser Arg His Pro Pro Glu Asn Gly Lys Pro Asn Ile  
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 50:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 50:

Ile Asn Thr Lys Cys Tyr Lys Leu Glu His Pro Val Thr Gly Cys Gly  
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 51:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 14  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear



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(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 51:

Tyr Lys Leu Asn Phe Tyr Phe Asp Leu Leu Arg Ala Lys Leu  
 1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 52:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 13  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS:  
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 52:

Ile Asp Thr Leu Lys Lys Asn Glu Asn Ile Lys Glu Leu  
 1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 53:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS:  
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 53:

Asp Val Gly Glu Tyr Arg Ala Val Thr Glu Leu Gly Arg Pro Asp Ala  
 1 5 10 15  
 Glu Tyr Trp Asn  
 20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 54:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS:  
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 54:

Glu Arg Phe Ala Val Asn Pro Gly Leu Leu Glu Thr Ser Glu Gly Cys  
 1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 55:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 23  
 (B) TYPE: amino acid

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(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 55:

Asp Asn Tyr Arg Gly Tyr Ser Leu Gly Asn Trp Val Cys Ala Ala Lys  
1 5 10 15  
Phe Glu Ser Asn Phe Thr Gln  
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 56:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 56:

Glu Ala Leu Val Arg Gln Gly Leu Ala Lys Val Ala Tyr Val Tyr Lys  
1 5 10 15  
Pro Asn Asn Thr  
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 57:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 57:

Pro Ile Val Gln Asn Leu Gln Gly Gln Met Val His Gln Ala Ile Ser  
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 58:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 58:

Ser Ala Leu Ser Glu Gly Ala Thr Pro Gln Asp Leu Asn Thr Met Leu  
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 59:

(i) SEQUENCE CHARACTERISTICS:

- 69 -

- (A) LENGTH: 16
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 59:

Ser Phe Tyr Ile Leu Ala His Thr Glu Phe Thr Pro Thr Glu Thr Asp  
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 60:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 16
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 60:

Lys Met Tyr Phe Asn Leu Ile Asn Thr Lys Cys Tyr Lys Leu Glu His  
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 61:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 18
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 61:

Val Gly Ser Asp Trp Arg Phe Leu Arg Gly Tyr His Gln Tyr Ala Tyr  
1 5 10 15  
Ala Asp

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 62:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 17
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 62:

Gly Ser Asp Trp Arg Phe Leu Arg Gly Tyr His Gln Tyr Ala Tyr Asp  
1 5 10 15  
Gly

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 63:

(i) SEQUENCE CHARACTERISTICS:

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- (A) LENGTH: 20
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 63:

Pro Pro Lys Pro Val Ser Lys Met Arg Met Ala Thr Pro Leu Leu Met  
 1 5 10 15  
 Gln Ala Leu Pro  
 20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 64:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 19
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 64:

Lys Met Arg Met Ala Thr Pro Leu Leu Met Gln Ala Leu Pro Met Gly  
 1 5 10 15  
 Ala Leu Pro

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 65:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 23
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 65:

Glu His His Ile Phe Leu Gly Ala Thr Asn Tyr Ile Tyr Val Leu Asn  
 1 5 10 15  
 Glu Glu Asp Leu Gln Lys Val  
 20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 66:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 17
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 66:

Gln Glu Leu Lys Asn Lys Tyr Tyr Gln Val Pro Arg Lys Gly Ile Gln  
 1 5 10 15  
 Ala

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## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 67:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 67:

Ile Gln Asn Leu Ile Lys Glu Glu Ala Phe Leu Gly Ile Thr Asp Glu  
1 5 10 15  
Lys Thr Glu Gly  
20

## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 68:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 17
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 68:

Thr Ala Phe Gln Tyr Ile Ile Asp Asn Lys Gly Ile Asp Ser Asp Ala  
1 5 10 15  
Ser

## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 69:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 16
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 69:

Glu Pro Phe Leu Tyr Ile Leu Gly Lys Ser Arg Val Leu Glu Ala Gln  
1 5 10 15

## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 70:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 16
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 70:

Thr Leu Pro Pro Phe Gln Pro Gln Ile Thr Asp Asp Tyr Gly Leu Asp  
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 71:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 71:

Val Arg Trp Phe Arg Asn Gly Gln Glu Glu Lys Thr Gly Val Val Ser  
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 72:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 72:

Arg Val Gln Pro Lys Val Thr Val Tyr Pro Ser Lys Thr Gln Pro Leu  
1 5 10 15  
Gln His

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 73:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 15  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 73:

Arg Val Gln Pro Lys Val Thr Val Tyr Pro Ser Lys Thr Gln Pro  
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 74:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 19  
(B) TYPE: amino acid  
(C) STRANDEDNESS:

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(D) TOP LOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 74:

Asn Phe Leu Lys Ser Asp Gly Arg Ile Lys Tyr Thr Leu Asn Lys Asn  
1 5 10 15  
Ser Leu Lys

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 75:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 19  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 75:

Ile Pro Asp Asn Leu Phe Leu Lys Ser Asp Gly Arg Ile Lys Tyr Thr  
1 5 10 15  
Leu Asn Lys

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 76:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 76:

Asn Leu Phe Leu Lys Ser Asp Gly Arg Ile Lys Tyr Thr Leu Asn Lys  
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 77:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 15  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 77:

Asn Leu Phe Leu Lys Ser Asp Gly Arg Ile Lys Tyr Thr Leu Asn  
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 78:

(i) SEQUENCE CHARACTERISTICS:

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- (A) LENGTH: 17
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 78:

Tyr Ala Asn Ile Leu Leu Asp Arg Arg Val Pro Gln Thr Asp Met Thr  
1 5 10 15

Phe

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 79:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 18
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 79:

Gly Asp Thr Arg Pro Arg Phe Leu Glu Tyr Ser Thr Ser Glu Cys His  
1 5 10 15

Phe Phe

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 80:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 21
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 80:

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser  
1 5 10 15

Pro Val Thr Lys Ser  
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 81:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 81:

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser  
1 5 10 15

Pro Val Thr Lys  
20



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## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 82:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 18
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 82:

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro  
1 5 10 15  
Val Thr

## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 83:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 17
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 83:

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser  
1 5 10 15  
Pro

## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 84:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 17
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 84:

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser  
1 5 10 15  
Ser

## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 85:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 16
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 85:

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser  
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 86:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 16
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 86:

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro  
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 87:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 16
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 87:

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser  
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 88:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 15
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 88:

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser  
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 89:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 15
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 89:

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser  
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 90:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 14  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 90:

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly  
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 91:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 17  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 91:

Ala Pro Ser Pro Leu Pro Glu Thr Thr Glu Asn Val Val Cys Ala Leu  
1 5 10 15  
Gly

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 92:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 92:

Val Asp Asp Thr Gln Phe Val Arg Phe Asp Ser Asp Ala Ala Ser Gln  
1 5 10 15  
Arg Met Glu Pro Arg  
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 93:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20  
(B) TYPE: amino acid  
(C) STRANDEDNESS:

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(D) TOP LOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 93:

Val Asp Asp Thr Gln Phe Val Arg Phe Asp Ser Asp Ala Ala Ser Gln  
1 5 10 15  
Arg Met Glu Pro  
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 94:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 19  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 94:

Val Asp Asp Thr Gln Phe Val Arg Phe Asp Ser Asp Ala Ala Ser Gln  
1 5 10 15  
Arg Met Glu

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 95:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 19  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 95:

Asp Thr Gln Phe Val Arg Phe Asp Ser Asp Ala Ala Ser Gln Arg Met  
1 5 10 15  
Glu Pro Arg

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 96

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 19  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

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## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 96:

Thr Gln Phe Val Arg Phe Asp Ser Asp Ala Ala Ser Gln Arg Met Glu  
 1 5 10 15  
 Pro Arg Ala

## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 97:

## (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 17  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS:  
 (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 97:

Val Asp Asp Thr Gln Phe Val Arg Phe Asp Ser Asp Ala Ala Ser Gln  
 1 5 10 15  
 Arg

## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 98:

## (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 17  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS:  
 (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 98:

Thr Gln Phe Val Arg Phe Asp Ser Asp Ala Ala Ser Gln Arg Met Glu  
 1 5 10 15  
 Pro

## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 99:

## (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 15  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS:  
 (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 99:

Thr Gln Phe Val Arg Phe Asp Ser Asp Ala Ala Ser Gln Arg Met  
 1 5 10 15

## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 100:

## (i) SEQUENCE CHARACTERISTICS:

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- (A) LENGTH: 12
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 100:

Thr Gln Phe Val Arg Phe Asp Ser Asp Ala Ala Ser  
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 101:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 23
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 101:

Val Asp Asp Thr Gln Phe Val Arg Phe Asp Ser Asp Ala Ala Ser Pro  
1 5 10 15  
Arg Gly Glu Pro Arg Ala Pro  
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 102:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 22
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 102:

Thr Gln Phe Val Arg Phe Asp Ser Asp Ala Ala Ser Pro Arg Gly Glu  
1 5 10 15  
Pro Arg Ala Pro Trp Val  
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 103:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 21
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 103:

Val Asp Asp Thr Gln Phe Val Arg Phe Asp Ser Asp Ala Ala Ser Pro  
1 5 10 15  
Arg Gly Glu Pro Arg  
20

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## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 104:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 104:

Val Asp Asp Thr Gln Phe Val Arg Phe Asp Ser Asp Ala Ala Ser Pro  
1 5 10 15  
Arg Gly Glu Pro  
20

## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 105:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 19
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 105:

Val Asp Asp Thr Gln Phe Val Arg Phe Asp Ser Asp Ala Ala Ser Pro  
1 5 10 15  
Arg Gly Glu

## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 106:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 18
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 106:

Val Asp Asp Thr Gln Phe Val Arg Phe Asp Ser Asp Ala Ala Ser Pro  
1 5 10 15  
Arg Gly

## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 107:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 18
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 107:

Thr Gln Phe Val Arg Phe Asp Ser Asp Ala Ala Ser Pro Arg Gly Glu  
1 5 10 15  
Pro Arg

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 108:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 17  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 108:

Val Asp Asp Thr Gln Phe Val Arg Phe Asp Ser Asp Ala Ala Ser Pro  
1 5 10 15  
Arg

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 109:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 17  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 109:

Asp Thr Gln Phe Val Arg Phe Asp Ser Asp Ala Ala Ser Pro Arg Gly  
1 5 10 15  
Glu

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 110:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 14  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 110:

Thr Gln Phe Val Arg Phe Asp Ser Asp Ala Ala Ser Pro Arg  
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 111:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 12



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(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 111:

Thr Gln Phe Val Arg Phe Asp Ser Asp Ala Ala Ser  
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 112:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 112:

Leu Arg Ser Trp Thr Ala Ala Asp Thr Ala Ala Gln Ile Thr Gln Arg  
1 5 10 15  
Lys Trp Glu Ala Ala  
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 113:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 17  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 113:

Asp Leu Arg Ser Trp Thr Ala Ala Asp Thr Ala Ala Gln Ile Thr Gln  
1 5 10 15  
Arg

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 114:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 114:

Asp Leu Arg Ser Trp Thr Ala Ala Asp Thr Ala Ala Gln Ile Thr Gln  
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 115:

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## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 15
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 115:

Asp Leu Arg Ser Trp Thr Ala Ala Asp Thr Ala Ala Gln Ile Thr  
1 5 10 15

## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 116:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 17
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 116:

Asp Leu Ser Ser Trp Thr Ala Ala Asp Thr Ala Ala Gln Ile Thr Gln  
1 5 10 15

Arg

## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 117:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 117:

Asp Leu Ser Ser Trp Thr Ala Ala Asp Thr Ala Ala Gln Ile Thr Gln  
1 5 10 15

Arg Lys Trp Glu  
20

## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 118:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 17
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

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## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 118:

Tyr Asp His Asn Phe Val Lys Ala Ile Asn Ala Asp Gln Lys Ser Trp  
1                      5                      10                      15  
Thr

## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 119:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 17
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 119:

Tyr Asp His Asn Phe Val Lys Ala Ile Asn Ala Asp Ile Lys Ser Trp  
1                      5                      10                      15  
Thr

## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 120:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 16
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 120:

Tyr Asp His Asn Phe Val Lys Ala Ile Asn Ala Asp Gln Lys Ser Trp  
1                      5                      10                      15

## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 121:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 16
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 121:

Tyr Asp His Asn Phe Val Lys Ala Ile Asn Ala Ile Gln Lys Ser Trp  
1                      5                      10                      15

## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 122:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 14
- (B) TYPE: amino acid
- (C) STRANDEDNESS:

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(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 122:

Gly Asp Thr Arg Pro Arg Phe Leu Glu Gln Val Lys His Glu  
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 123:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 17  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 123:

Gly Val Tyr Phe Tyr Leu Gln Trp Gly Arg Ser Thr Leu Val Ser Val  
1 5 10 15

Ser

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 124:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 124:

Arg Pro Ala Gly Asp Gly Thr Phe Gln Lys Trp Ala Ser Val Val Val  
1 5 10 15

Pro Ser Gly Gln  
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 125:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 125:

Arg Pro Ala Gly Asp Gly Thr Phe Gln Lys Trp Ala Ser Val Val Val  
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 126:

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## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 22
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 126:

Gly Asp Gly Thr Phe Gln Lys Trp Ala Ser Val Val Val Pro Ser Gly  
1 5 10 15  
Gln Glu Gln Arg Tyr Thr  
20

## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 127:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 18
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 127:

Gly Asp Gly Thr Phe Gln Lys Trp Ala Ser Val Val Val Pro Ser Gly  
1 5 10 15  
Gln Glu

## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 128:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 14
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 128:

Gly Thr Phe Gln Lys Trp Ala Ser Val Val Val Pro Ser Gly  
1 5 10

## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 129:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 15
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 129:

Gly Thr Ph Gln Lys Trp Ala Ser Val Val Val Pro Ser Gly Gln  
1 5 10 15

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## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 130:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 23
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 130:

Gly Thr Phe Gln Lys Trp Ala Ser Val Val Val Pro Ser Gly Gln Glu  
1 5 10 15  
Gln Arg Tyr Thr Cys His Val  
20

## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 131:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 21
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 131:

Gly Ala Leu Ala Asn Ile Ala Val Asp Lys Ala Asn Leu Glu Ile Met  
1 5 10 15  
Thr Lys Arg Ser Asn  
20

## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 132:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 17
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 132:

Thr Pro Ser Tyr Val Ala Phe Thr Asp Thr Glu Arg Leu Ile Gly Asp  
1 5 10 15  
Ala

## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 133:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 15
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 133:

Thr Pro Ser Tyr Val Ala Phe Thr Asp Thr Glu Arg Leu Ile Gly  
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 134:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 16
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 134:

Arg Ser Glu Glu Phe Leu Ile Ala Gly Lys Leu Gln Asp Gly Leu Leu  
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 135:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 15
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 135:

Ser Glu Glu Phe Leu Ile Ala Gly Lys Leu Gln Asp Gly Leu Leu  
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 136:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 15
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 136:

Asp Val Ile Trp Glu Leu Leu Asn His Ala Gln Glu His Phe Gly  
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 137:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 16
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 137:

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Glu Pro Phe Leu Tyr Ile Leu Gly Lys Ser Arg Val Leu Glu Ala Gln  
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 138:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 15  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 138:

Thr Ala Phe Gln Tyr Ile Ile Asp Asn Lys Gly Ile Asp Ser Asp  
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 139:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 14  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 139:

Thr Ala Phe Gln Tyr Ile Ile Asp Asn Lys Gly Ile Asp Ser  
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 140:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 24  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 140:

Ser Glu Thr Val Phe Leu Pro Arg Glu Asp His Leu Phe Arg Lys Phe  
1 5 10 15

His Tyr Leu Pro Phe Leu Pro Ser  
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 141:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear



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(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 141:

Val Phe Leu Pro Arg Glu Asp His Leu Phe Arg Lys Phe His Tyr Leu  
 1 5 10 15  
 Pro Phe Leu Pro Ser  
 20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 142:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS:  
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 142:

Val Phe Leu Pro Arg Glu Asp His Leu Phe Arg Lys Phe His Tyr Leu  
 1 5 10 15  
 Pro Phe Leu Pro  
 20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 143:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS:  
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 143:

Val Phe Leu Pro Arg Glu Asp His Leu Phe Arg Lys Phe His Tyr Leu  
 1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 144:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 26  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS:  
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 144:

Lys Leu Gly His Pro Asp Thr Leu Asn Gln Gly Glu Phe Lys Glu Leu  
 1 5 10 15

Val Arg Lys Asp Leu Gln Asn Phe Leu Lys  
 20 25

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 145:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 24

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(B) TYPE: amino acid  
 (C) STRANDEDNESS:  
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 145:

Lys Leu Gly His Pro Asp Thr Leu Asn Gln Gly Glu Phe Lys Glu Leu  
 1 5 10 15  
 Val Arg Lys Asp Leu Gln Asn Phe  
 20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 146:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 14  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS:  
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 146:

Lys Leu Gly His Pro Asp Thr Leu Asn Gln Gly Glu Phe Lys  
 1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 147:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 123  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 147:

ATG GCC ATA AGT GGA GTC CCT GTG CTA GGA TTT TTC ATC ATA GCT GTG	48
Met Ala Ile Ser Gly Val Pro Val Leu Gly Phe Phe Ile Ile Ala Val	
1 5 10 15	
CTG ATG AGC GCT CAG GAA TCA TGG GCT AAG ATG CGC ATG GCC ACC CCG	96
Leu Met Ser Ala Gln Glu Ser Trp Ala Lys Met Arg Met Ala Thr Pro	
20 25 30	
CTG CTG ATG CAG GCG CTG CCC ATG TAA	123
Leu Leu Met Gln Ala Leu Pro Met	
35 40	

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 148:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 150  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

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## (xi) SEQUENCE DESCRIPTI N: SEQ ID NO: 148:

ATG GCC ATA AGT GGA GTC CCT GTG CTA GGA TTT TTC ATC ATA GCT GTG	48
Met Ala Ile Ser Gly Val Pro Val Leu Gly Phe Phe Ile Ile Ala Val	
1 5 10 15	
CTG ATG AGC GCT CAG GAA TCA TGG GCT CTT CCC AAG CCT CCC AAG CCT	96
Leu Met Ser Ala Gln Glu Ser Trp Ala Leu Pro Lys Pro Pro Lys Pro	
20 25 30	
GTG AGC AAG ATG CGC ATG GCC ACC CCG CTG CTG ATG CAG GCG CTG CCC	144
Val Ser Lys Met Arg Met Ala Thr Pro Leu Leu Met Gln Ala Leu Pro	
35 40 45	
ATG TAA	150
Met	

## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 149:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 10
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 149:

Thr Gln Phe Val Arg Phe Asp Ser Asp Ala
1 5 10

## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 150:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 10
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 150:

Asp Trp Arg Phe Leu Arg Gly Tyr His Gln
1 5 10

## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 151:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 10
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 151:

Arg Met Ala Thr Pro Leu Leu Met Gln Ala
1 5 10

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(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 152:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 4  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 152:

Lys Asp Glu Leu  
1

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 153:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 5  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 153:

Lys Phe Glu Arg Gln  
1 5

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 154:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 5  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 154:

Gln Arg Glu Phe Lys  
1 5

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 155:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 25  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 155:

Met Ala Ile Ser Gly Val Pro Val Leu Gly Phe Phe Ile Ile Ala Val  
1 5 10 15

Leu Met Ser Ala Gln Glu Ser Trp Ala  
20 25

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## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 156:

## (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 14  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 156:

Met Arg Met Ala Thr Pro Leu Leu Met Gln Ala Leu Pro Met  
1 5 10

## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 157:

## (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 23  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 157:

Met Pro Arg Ser Arg Ala Leu Ile Leu Gly Val Leu Ala Leu Thr Thr  
1 5 10 15  
Met Leu Ser Leu Cys Gly Gly  
20

## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 158:

## (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 23  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 158:

Asn Ile Val Ile Lys Arg Ser Asn Ser Thr Ala Ala Thr Asn Glu Val  
1 5 10 15  
Pro Glu Val Thr Val Phe Ser  
20

## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 159:

## (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 159:

Asn Ile Val Ile Lys Arg Ser Asn Ser Thr Ala Ala Thr Asn Glu Val  
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 160:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 18
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 160:

Ser Asp Val Gly Val Tyr Arg Ala Val Thr Pro Gln Gly Arg Pro Asp  
1 5 10 15

Ala Glu

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 161:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 17
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 161:

Asp Val Gly Val Tyr Arg Ala Val Thr Pro Gln Gly Arg Pro Asp Ala  
1 5 10 15

Glu

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 162:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 15
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 162:

Asp Val Gly Val Tyr Arg Ala Val Thr Pro Gln Gly Arg Pro Asp  
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 163:

(i) SEQUENCE CHARACTERISTICS:

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(A) LENGTH: 13  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 163:

Ala Pro Ser Pro Leu Pro Glu Thr Thr Glu Asn Val Val  
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 164:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 17  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 164:

Ala Pro Ser Pro Leu Pro Glu Thr Thr Glu Asn Val Val Cys Ala Leu  
1 5 10 15

Gly

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 165:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 165:

Phe Pro Lys Ser Leu His Thr Tyr Ala Asn Ile Leu Leu Asp Arg Arg  
1 5 10 15

Val Pro Gln Thr Asp  
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 166:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 19  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 166:

Phe Pro Lys Ser Leu His Thr Tyr Ala Asn Ile Leu Leu Asp Arg Arg  
 1                      5                      10                      15  
 Val Pro Gln

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 167:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS:  
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 167:

Asp Gly Ile Leu Tyr Tyr Tyr Gln Ser Gly Gly Arg Leu Arg Arg Pro  
 1                      5                      10                      15  
 Val Asn

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 168:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 17  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS:  
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 168:

Asp Gly Ile Leu Tyr Tyr Tyr Gln Ser Gly Gly Arg Leu Arg Arg Pro  
 1                      5                      10                      15  
 Val

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 169:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 30  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS:  
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 169:

Leu Ser Pro Ile His Ile Ala Leu Asn Phe Ser Leu Asp Pro Gln Ala  
 1                      5                      10                      15  
 Pro Val Asp Ser His Gly Leu Arg Pro Ala Leu His Tyr Gln  
 20                      25                      30



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## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 170:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 16
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 170:

Leu Trp Asp Tyr Gly Met Ser Ser Ser Pro His Val Leu Arg Asn Arg  
1 5 10 15

## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 171:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 16
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 171:

Val Asp Asp Thr Gln Phe Val Arg Phe Asp Ser Asp Ala Ala Ser Gln  
1 5 10 15

## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 172:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 19
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 172:

Pro Pro Glu Val Thr Val Leu Thr Asn Ser Pro Val Glu Leu Arg Glu  
1 5 10 15

Pro Asn Val

## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 173:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 18
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

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(xi) SEQUENCE DESCRIPTI N: SEQ ID NO: 173:

Pro Pro Glu Val Thr Val Leu Thr Asn Ser Pro Val Glu Leu Arg Glu  
 1                      5                      10                      15  
 Pro Asn

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 174:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 16
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 174:

Val Phe Leu Leu Leu Leu Ala Asp Lys Val Pro Glu Thr Ser Leu Ser  
 1                      5                      10                      15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 175:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 16
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 175:

Thr Phe Asp Glu Ile Ala Ser Gly Phe Arg Gln Gly Gly Ala Ser Gln  
 1                      5                      10                      15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 176:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 14
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 176:

Tyr Gly Tyr Thr Ser Tyr Asp Thr Phe Ser Trp Ala Phe Leu  
 1                      5                      10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 177:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 19
- (B) TYPE: amino acid
- (C) STRANDEDNESS:

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(D) TOP LOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 177:

Ala Thr Lys Tyr Gly Asn Met Thr Glu Asp His Val Met His Leu Leu  
1 5 10 15

Gln Asn Ala

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 178:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 14  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 178:

Gly Gln Val Lys Lys Asn Asn His Gln Glu Asp Lys Ile Glu  
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 179:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 13  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 179:

Leu Asn Lys Ile Leu Leu Asp Glu Gln Ala Gln Trp Lys  
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 180:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 180:

Gly Pro Pro Lys Leu Asp Ile Arg Lys Glu Glu Lys Gln Ile Met Ile  
1 5 10 15

Asp Ile Phe His  
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 181:

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## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 21
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 181:

Gly Pro Pro Lys Leu Asp Ile Arg Lys Glu Glu Lys Gln Ile Met Ile  
1 5 10 15

Asp Ile Phe His Pro  
20

## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 182:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 22
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 182:

Ser Pro Leu Gln Ala Leu Asp Phe Phe Gly Asn Gly Pro Pro Val Asn  
1 5 10 15

Tyr Lys Thr Gly Asn Leu  
20

## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 183:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 183:

Ser Pro Leu Gln Ala Leu Asp Phe Phe Gly Asn Gly Pro Pro Val Asn  
1 5 10 15

Tyr Lys Thr Gly  
20

## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 184:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 18
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 184:

Gly Lys Phe Ala Ile Arg Pro Asp Lys Lys Ser Asn Pro Ile Ile Arg  
1 5 10 15

Thr Val

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 185:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 15
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 185:

Thr Gly His Gly Ala Arg Thr Ser Thr Glu Pro Thr Thr Asp Tyr  
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 186:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 13
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 186:

Lys Glu Leu Lys Arg Gln Tyr Glu Lys Lys Leu Arg Gln  
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 187:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 12
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 187:

Asp Asp Thr Gln Phe Val Arg Phe Asp Ser Asp Ala  
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 188:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 16
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOP LOGY: linear

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 188:

Gly Pro Asp Gly Arg Leu Leu Arg Gly His Asn Gln Tyr Asp Gly Lys  
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 189:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 14
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 189:

Ile Ala Leu Leu Leu Met Ala Ser Gln Glu Pro Gln Arg Met  
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 190:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 190:

Ile Ala Leu Leu Leu Met Ala Ser Gln Glu Pro Gln Arg Met Ser Arg  
1 5 10 15

Asn Phe Val Arg  
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 191:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 191:

Ile Pro Asp Asn Leu Phe Leu Lys Ser Asp Gly Arg Ile Lys Tyr Thr  
1 5 10 15

Leu Asn Lys Asn  
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 192:

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## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 18
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 192:

Ile Pro Asp Asn Leu Phe Leu Lys Ser Asp Gly Arg Ile Lys Tyr Thr  
1 5 10 15

Leu Asn

## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 193:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 17
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 193:

Ile Pro Asp Asn Leu Phe Leu Lys Ser Asp Gly Arg Ile Lys Tyr Thr  
1 5 10 15

Leu

## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 194:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 17
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 194:

Val Thr Thr Leu Asn Ser Asp Leu Lys Tyr Asn Ala Leu Asp Leu Thr  
1 5 10 15

Asn

## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 195:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 23
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOP LOGY: linear

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 195:

Val Asp Asp Thr Gln Phe Val Arg Phe Asp Ser Asp Ala Ala Ser Gln  
1 5 10 15  
Arg Met Glu Pro Arg Ala Pro  
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 196:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 13
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 196:

Asp Val Ile Trp Glu Leu Leu Asn His Ala Gln Glu His  
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 197:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 19
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 197:

Asp Leu Arg Ser Trp Thr Ala Ala Asp Thr Ala Ala Gln Ile Thr Gln  
1 5 10 15  
Arg Lys Trp

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 198:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 18
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 198:

Leu Arg Ser Trp Thr Ala Ala Asp Thr Ala Ala Gln Ile Thr Gln Arg  
1 5 10 15  
Lys Trp



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## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 199:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 22
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 199:

Asp Leu Ser Ser Trp Thr Ala Ala Asp Thr Ala Ala Gln Ile Thr Gln  
1 5 10 15  
Arg Lys Trp Glu Ala Ala  
20

## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 200:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 18
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 200:

Asp Leu Ser Ser Trp Thr Ala Ala Asp Thr Ala Ala Gln Ile Thr Gln  
1 5 10 15  
Arg Lys

## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 201:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 201:

Gly Ser Leu Phe Val Tyr Asn Ile Thr Thr Asn Lys Tyr Lys Ala Phe  
1 5 10 15  
Leu Asp Lys Gln  
20

## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 202:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 16
- (B) TYPE: amino acid

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(C) STRANDEDNESS:

(D) TOPOLOGY: lin ar

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 202:

Gly Ser Leu Phe Val Tyr Asn Ile Thr Thr Asn Lys Tyr Lys Ala Phe  
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 203:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 203:

Ala Ala Pro Tyr Glu Lys Glu Val Pro Leu Ser Ala Leu Thr Asn Ile  
1 5 10 15  
Leu Ser Ala Gln Leu  
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 204:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 204:

Ala Ala Pro Tyr Glu Lys Glu Val Pro Leu Ser Ala Leu Thr Asn Ile  
1 5 10 15  
Leu Ser

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 205:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 205:

Ala Glu Ala Leu Glu Arg Met Phe Leu Ser Phe Pro Thr Thr Lys Thr  
1 5 10 15

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## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 206:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 15
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 206:

Ser Pro Glu Asp Phe Val Tyr Gln Phe Lys Gly Met Cys Tyr Phe  
1 5 10 15

## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 207:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 207:

Ser Asp Trp Arg Phe Leu Arg Gly Tyr His Gln Tyr Ala Tyr Asp Gly  
1 5 10 15  
Lys Asp Tyr Ile  
20

## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 208:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 14
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 208:

Gly Ser Asp Trp Arg Phe Leu Arg Gly Tyr His Gln Tyr Ala  
1 5 10

## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 209:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 13
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

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(xi) SEQUENCE DESCRIPTI N: SEQ ID NO: 209:

Gly Ser Asp Trp Arg Phe Leu Arg Gly Tyr His Gln Tyr  
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 210:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 13
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 210:

Ser Asp Trp Arg Phe Leu Arg Gly Tyr His Gln Tyr Ala  
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 211:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 17
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 211:

Arg Glu Thr Gln Ile Ser Lys Thr Asn Thr Gln Thr Tyr Arg Glu Asn  
1 5 10 15  
Leu

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 212:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 16
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 212:

Arg Glu Thr Gln Ile Ser Lys Thr Asn Thr Gln Thr Tyr Arg Glu Asn  
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 213:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 15
- (B) TYPE: amino acid

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(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 213:

Arg Glu Thr Gln Ile Ser Lys Thr Asn Thr Gln Thr Tyr Arg Glu  
 1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 214:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 26

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 214:

Arg Ser Asn Tyr Thr Pro Ile Thr Asn Pro Pro Glu Val Thr Val Leu  
 1 5 10 15

Thr Asn Ser Pro Val Glu Leu Arg Glu Pro  
 20 25

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 215:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 215:

Ala Pro Ser Pro Leu Pro Glu Thr Thr Glu Asn Val Val Cys Ala Leu  
 1 5 10 15

Gly Leu Thr Val  
 20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 216:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 30

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 216:

Ser Leu Gln Ser Pro Ile Thr Val Glu Trp Arg Ala Gln Ser Glu Ser  
 1 5 10 15

Ala Gln Ser Lys Met Leu Ser Gly Ile Gly Gly Phe Val Leu  
 20 25 30

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## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 217:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 21
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 217:

Val Thr Gln Tyr Leu Asn Ala Thr Gly Asn Arg Trp Cys Ser Trp Ser  
1 5 10 15  
Leu Ser Gln Ala Arg  
20

## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 218:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 17
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 218:

Val Thr Gln Tyr Leu Asn Ala Thr Gly Asn Arg Trp Cys Ser Trp Ser  
1 5 10 15  
Leu

## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 219:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 13
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 219:

Thr Ser Ile Leu Cys Tyr Arg Lys Arg Glu Trp Ile Lys  
1 5 10

## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 220:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 14
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 220:

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu  
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 221:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 13  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 221:

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly  
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 222:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 25  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 222:

Gly Asp Met Tyr Pro Lys Thr Trp Ser Gly Met Leu Val Gly Ala Leu  
1 5 10 15

Cys Ala Leu Ala Gly Val Leu Thr Ile  
20 25

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 223:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 19  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 223:

Ala Pro Val Leu Ile Ser Gln Lys Leu Ser Pro Ile Tyr Asn Leu Val  
1 5 10 15

Pro Val Lys

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 224:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 15

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(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 224:

Pro Ala Phe Arg Phe Thr Arg Glu Ala Ala Gln Asp Cys Glu Val  
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 225:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 225:

Val Pro Gly Leu Tyr Ser Pro Cys Arg Ala Phe Phe Asn Lys Glu Glu  
1 5 10 15

Leu Leu

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 226:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 14  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 226:

Val Pro Gly Leu Tyr Ser Pro Cys Arg Ala Phe Phe Asn Lys  
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 227:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 23  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 227:

Lys Val Asp Leu Thr Phe Ser Lys Gln His Ala Leu Leu Cys Ser Asp  
1 5 10 15

Tyr Gln Ala Asp Tyr Glu Ser  
20



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## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 228:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 15
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 228:

Lys Val Asp Leu Thr Phe Ser Lys Gln His Ala Leu Leu Cys Ser  
1 5 10 15

## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 229:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 13
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 229:

Phe Ser His Asp Tyr Arg Gly Ser Thr Ser His Arg Leu  
1 2 10

## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 230:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 13
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 230:

Leu Pro Lys Tyr Phe Glu Lys Lys Arg Asn Thr Ile Ile  
1 5 10

## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 231:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 23
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 231:

Ser Glu Thr Val Phe Leu Pro Arg Glu Asp His Leu Phe Arg Lys Phe  
1 5 10 15  
His Tyr Leu Pro Phe Leu Pro  
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 232:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 18
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 232:

Ala Pro Ser Pro Leu Pro Glu Glu Thr Thr Glu Asn Val Val Cys Ala  
1 5 10 15  
Leu Gly

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 233:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 24
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 233:

Gly Asp Thr Arg Pro Arg Phe Leu Glu Tyr Ser Thr Gly Glu Cys Tyr  
1 5 10 15  
Phe Phe Asn Gly Thr Glu Arg Val  
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 234:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 13
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 234:

Arg His Asn Tyr Glu Leu Asp Glu Ala Val Thr Leu Gln  
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 235:

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## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 21
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 235:

Asp Pro Gln Ser Gly Ala Leu Tyr Ile Ser Lys Val Gln Lys Glu Asp  
1 5 10 15

Asn Ser Thr Tyr Ile  
20

## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 236:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 17
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 236:

Gly Ala Leu Tyr Ile Ser Lys Val Gln Lys Glu Asp Asn Ser Thr Tyr  
1 5 10 15  
Ile

## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 237:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 18
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 237:

Asp Pro Val Pro Lys Pro Val Ile Lys Ile Glu Lys Ile Glu Asp Met  
1 5 10 15  
Asp Asp

## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 238:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 15
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 238:

Asp Pro Val Pro Lys Pro Val Ile Lys Ile Glu Lys Ile Glu Asp  
 1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 239:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 18
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 239:

Phe Thr Phe Thr Ile Ser Arg Leu Glu Pro Glu Asp Phe Ala Val Tyr  
 1 5 10 15

Tyr Cys

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 240:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 15
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 240:

Phe Thr Phe Thr Ile Ser Arg Leu Glu Pro Glu Asp Phe Ala Val  
 1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 241:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 14
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 241:

Asp Pro Val Glu Met Arg Arg Leu Asn Tyr Gln Thr Pro Gly  
 1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 242:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 18
- (B) TYPE: amino acid

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(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 242:

Tyr Gln Leu Leu Arg Ser Met Ile Gly Tyr Ile Glu Glu Leu Ala Pro  
1 5 10 15  
Ile Val

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 243:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 17  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 243:

Gly Asn His Leu Tyr Lys Trp Lys Gln Ile Pro Asp Cys Glu Asn Val  
1 5 10 15  
Lys

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 244:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 244:

Leu Pro Phe Phe Leu Phe Arg Gln Ala Tyr His Pro Asn Asn Ser Ser  
1 5 10 15  
Pro Val Cys Tyr  
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 245:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 28  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 245:

Gln Ala Lys Phe Phe Ala Cys Ile Lys Arg Ser Asp Gly Ser Cys Ala  
1 5 10 15  
Trp Tyr Arg Gly Ala Ala Pro Pro Lys Gln Glu Phe  
20 25

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 246:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 19
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 246:

Gln Ala Lys Phe Phe Ala Cys Ile Lys Arg Ser Asp Gly Ser Cys Ala  
1 5 10 15  
Trp Tyr Arg

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 247:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 15
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 247:

Ser Glu Glu Phe Leu Ile Ala Gly Lys Leu Gln Asp Gly Leu Leu  
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 248:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 12
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 248:

Asn Arg Ser Glu Glu Phe Leu Ile Ala Gly Lys Leu  
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 249:

(i) SEQUENCE CHARACTERISTICS:

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(A) LENGTH: 24  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 249:

Gln Asn Phe Thr Val Ile Phe Asp Thr Gly Ser Ser Asn Leu Trp Val  
1 5 10 15  
Pro Ser Val Tyr Cys Thr Ser Pro  
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 250:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 250:

Asp Glu Tyr Tyr Arg Arg Leu Leu Arg Val Leu Arg Ala Arg Glu Gln  
1 5 10 15  
Ile Val

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 251:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 17  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 251:

Glu Ala Ile Tyr Asp Ile Cys Arg Arg Asn Leu Asp Ile Glu Arg Pro  
1 5 10 15  
Thr

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 252:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 13  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 252:

Glu Ala Ile Tyr Asp Ile Cys Arg Arg Asn Leu Asp Ile  
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 253:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 253:

His Glu Leu Glu Lys Ile Lys Lys Gln Val Glu Gln Glu Lys Cys Glu  
1 5 10 15  
Ile Gln Ala Ala Leu  
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 254:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 10  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 254:

Arg Pro Ser Met Leu Gln His Leu Leu Arg  
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 255:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 22  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 255:

Asp Asp Phe Met Gly Gln Leu Leu Asn Gly Arg Val Leu Phe Pro Val  
1 5 10 15  
Asn Leu Gln Leu Gly Ala  
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 256:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 17  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear



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(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 256:

Ile Pro Arg Leu Gln Lys Ile Trp Lys Asn Tyr Leu Ser Met Asn Lys  
1 5 10 15  
Tyr

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 257:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 14  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 257:

Lys Arg Ser Phe Phe Ala Leu Arg Asp Gln Ile Pro Asp Leu  
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 258:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 17  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 258:

Arg Gln Tyr Arg Leu Lys Lys Ile Ser Lys Glu Glu Lys Thr Pro Gly  
1 5 10 15  
Cys

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 259:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 13  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 259:

Ala Glu Val Tyr His Asp Val Ala Ala Ser Glu Phe Phe  
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 260:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 19

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(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 260:

Asp Arg Pro Phe Leu Phe Val Val Arg His Asn Pro Thr Gly Thr Val  
1 5 10 15  
Leu Phe Met

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 261:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 261:

Met Pro His Phe Phe Arg Leu Phe Arg Ser Thr Val Lys Gln Val Asp  
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 262:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 262:

Lys Asn Ile Phe His Phe Lys Val Asn Gln Glu Gly Leu Lys Leu Ser  
1 5 10 15  
Asn Asp Met Met  
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 263:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 263:

Lys Asn Ile Phe His Phe Lys Val Asn Gln Glu Gly Leu Lys Leu Ser  
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 264:

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## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 264:

Tyr Lys Gln Thr Val Ser Leu Asp Ile Gln Pro Tyr Ser Leu Val Thr  
1 5 10 15  
Thr Leu Asn Ser  
20

## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 265:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 17
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 265:

Ser Thr Pro Glu Phe Thr Ile Leu Asn Thr Leu His Ile Pro Ser Phe  
1 5 10 15  
Thr

## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 266:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 18
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 266:

Thr Pro Glu Phe Thr Ile Leu Asn Thr Leu His Ile Pro Ser Phe Thr  
1 5 10 15  
Ile Asp

## (2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 267:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 16
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 267:

Thr Pro Glu Phe Thr Ile Leu Asn Thr Leu His Ile Pro Ser Phe Thr  
 1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 268:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 16
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 268:

Ser Asn Thr Lys Tyr Phe His Lys Leu Asn Ile Pro Gln Leu Asp Phe  
 1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 269:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 17
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 269:

Leu Pro Phe Phe Lys Phe Leu Pro Lys Tyr Phe Glu Lys Lys Arg Asn  
 1 5 10 15

Thr

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 270:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 15
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 270:

Leu Pro Phe Phe Lys Phe Leu Pro Lys Tyr Phe Glu Lys Lys Arg  
 1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 271:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 15

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(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 271:

Trp Asn Phe Tyr Tyr Ser Pro Gln Ser Ser Pro Asp Lys Lys Leu  
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 272:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 272:

Asp Val Ile Trp Glu Leu Leu Asn His Ala Gln Glu His Phe Gly Lys  
1 5 10 15  
Asp Lys Ser Lys Glu  
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 273:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 273:

Asp Val Ile Trp Glu Leu Leu Ile Asn His Ala Gln Glu His Phe Gly  
1 5 10 15

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CLAIMS

1. A purified preparation of a peptide consisting essentially of an amino acid sequence identical to that of a segment of a naturally-occurring human protein, said segment being of 10 to 30 residues in length, inclusive, wherein said peptide binds to a human major histocompatibility complex (MHC) class II allotype.
2. The preparation of claim 1, wherein said peptide binds to at least two distinct MHC class II allotypes.
3. The preparation of claim 1, wherein said human protein is HLA-A2, HLA-A29, HLA-A30, HLA-B44, HLA-B51, HLA-Bw62, HLA-C, HLA-DP  $\beta$ -chain, HLA-DQ  $\alpha$ -chain, HLA-DQ  $\beta$ -chain, HLA-DQ3.2  $\beta$ -chain, HLA-DR  $\alpha$ -chain, HLA-DR  $\beta$ -chain, HLA-DR4  $\beta$ -chain, invariant chain (Ii), Ig kappa chain, Ig kappa chain C region, Ig heavy chain, Na<sup>+</sup>/K<sup>+</sup> ATPase, potassium channel protein, sodium channel protein, calcium release channel protein, complement C9, glucose-transport protein, CD35, CD45, CD75, vinculin, calgranulin B, kinase C  $\zeta$ -chain, integrin  $\beta$ -4 gp150, hemoglobin, tubulin  $\alpha$ -1 chain, myosin  $\beta$ -heavy chain,  $\alpha$ -enolase, transferrin, transferrin receptor, fibronectin receptor  $\alpha$ -chain, acetylcholine receptor, interleukin-8 receptor, interferon  $\alpha$ -receptor, interferon  $\gamma$ -receptor, calcitonin receptor, LAM (lymphocyte activation marker) Blast-1, LAR (leukocyte antigen-related) protein, LIF (leukemia inhibitory factor) receptor, 4F2 cell-surface antigen (a cell-surface antigen involved in normal and neoplastic growth) heavy chain, cystatin SN, VLA-4 (a cell surface heterodimer in the integrin superfamily of adhesion receptors), PAI-1 (plasminogen activator inhibitor-1), IP-30 (interferon- $\gamma$  induced protein), ICAM-2, carboxypeptidase E, thromboxane-A synthase, NADH-cytochrome-b5 reductase, c-myc transforming protein, K-ras transforming protein, MET kinase-related

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transforming protein, interferon-induced guanylate-binding protein, mannose-binding protein, apolipoprotein B-100, cathepsin C, cathepsin E, cathepsin S, Factor VIII, von Willebrand factor, metalloproteinase inhibitor 1 precursor, metalloproteinase inhibitor 2, plasminogen activator inhibitor-1, or heat shock cognate 71 kD protein.

4. The preparation of claim 1, wherein said human protein is an MHC class I or II molecule.

5. The preparation of claim 1, wherein said segment conforms to the following motif:

at a first reference position (I) at or within 12 residues of the amino terminal residue of said segment, a positively charged residue or a large hydrophobic residue; and

at position I+5, a hydrogen bond donor residue.

6. The preparation of claim 5, wherein said motif comprises a hydrophobic residue at I+9.

7. The preparation of claim 6, wherein said motif additionally comprises, at position I+1 or I-1, a hydrophobic residue.

8. The preparation of claim 1, wherein said segment comprises residues 29-40 (SEQ ID NO: 187) or residues 106-115 (SEQ ID NO: 150) of HLA-A2.

9. The preparation of claim 1, wherein said segment comprises residues 107-116 of Ii (SEQ ID NO: 151).

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10. A liposome containing a peptide consisting essentially of an amino acid sequence identical to that of a segment of a naturally-occurring human protein, said segment being of 10 to 30 residues in length, wherein said peptide binds to a human major histocompatibility complex (MHC) class II allotype.

11. An immune-stimulating complex (ISCOM) comprising a peptide consisting essentially of an amino acid sequence identical to that of a segment of a naturally-occurring human protein, said segment being of 10 to 30 residues in length, wherein said peptide binds to a human major histocompatibility complex (MHC) class II allotype.

12. A nucleic acid encoding a polypeptide, said polypeptide comprising a first and a second amino acid sequence linked by a peptide bond, said first sequence being identical to that of a segment of a naturally-occurring human protein, which segment binds to a human MHC class II allotype and is of 10 to 30 residues in length; and said second sequence being a sequence which controls intracellular trafficking of a polypeptide to which it is attached ("trafficking sequence").

13. The nucleic acid of claim 12, wherein said trafficking sequence is KDEL (SEQ ID NO: 152); KFERQ (SEQ ID NO: 153); QREFK (SEQ ID NO: 154); MAISGVPVLGFFIIAVLMSAQESWA (SEQ ID NO: 155); a pentapeptide comprising Q flanked on one side by four residues selected from K, R, D, E, F, I, V, and L; or a signal peptide.

14. A nucleic acid encoding a polypeptide comprising a first and a second amino acid sequence linked by a peptide bond, said first sequence being identical to that



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of a segment of a naturally-occurring human protein, which segment binds to a human MHC class II allotype and is of 10 to 30 residues in length; and said second sequence being substantially identical to human Ii.

15. A cell comprising the nucleic acid molecule of claim 14.

16. A method of making a peptide, which method comprises culturing the cell of claim 15 under conditions permitting expression of said peptide from said nucleic acid molecule.

17. The preparation of claim 1, wherein said segment consists essentially of a sequence set forth in any of Tables 1-10.

18. A method of identifying a nonallelically restricted immunomodulating peptide, said method comprising:

- (a) fractionating a mixture of peptides eluted from a first MHC class II allotype;
- (b) identifying a self peptide from said mixture;
- (c) testing whether said self peptide binds to a second MHC class II allotype, said binding being an indication that said self peptide is a nonallelically restricted immunomodulating peptide.

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19. A method of identifying a potential immunomodulating peptide, said method comprising:

(a) providing a cell expressing MHC class II molecules on its surface;

(b) introducing into said cell a nucleic acid encoding a candidate peptide;

(c) determining whether the proportion of said class II molecules which are bound to said candidate peptide is increased in the presence of said nucleic acid compared to the proportion bound in the absence of said nucleic acid, said increase being an indication that said candidate peptide is a potential immunomodulating peptide.

20. A method of identifying a potential immunomodulating peptide, said method comprising:

(a) providing a cell expressing MHC class II molecules on its surface;

(b) introducing into said cell a nucleic acid encoding a candidate peptide;

(c) determining whether the level of MHC class II molecules on the surface of said cell is decreased in the presence of said nucleic acid compared to the level of said molecules in the absence of said nucleic acid, said decrease being an indication that said candidate peptide is a potential immunomodulating peptide.

21. A method of identifying a nonallelically restricted immunostimulating peptide, said method comprising:

(a) providing a cell bearing a first MHC class I or class II allotype, said cell being infected with a pathogen;

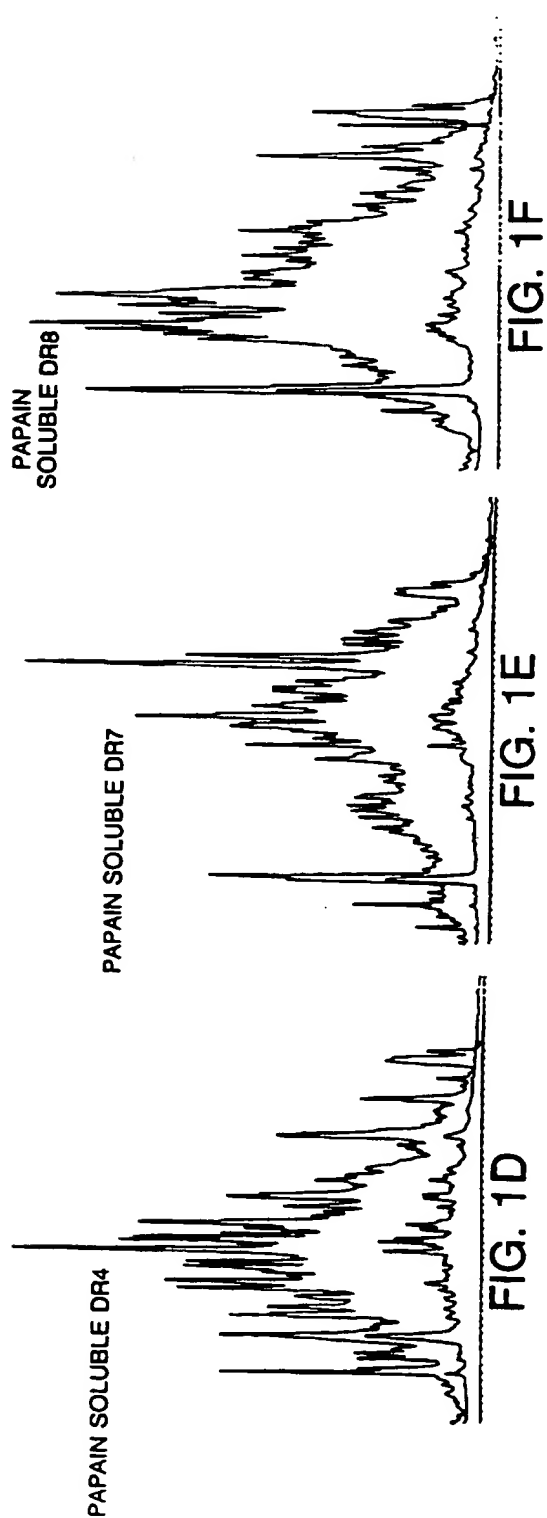
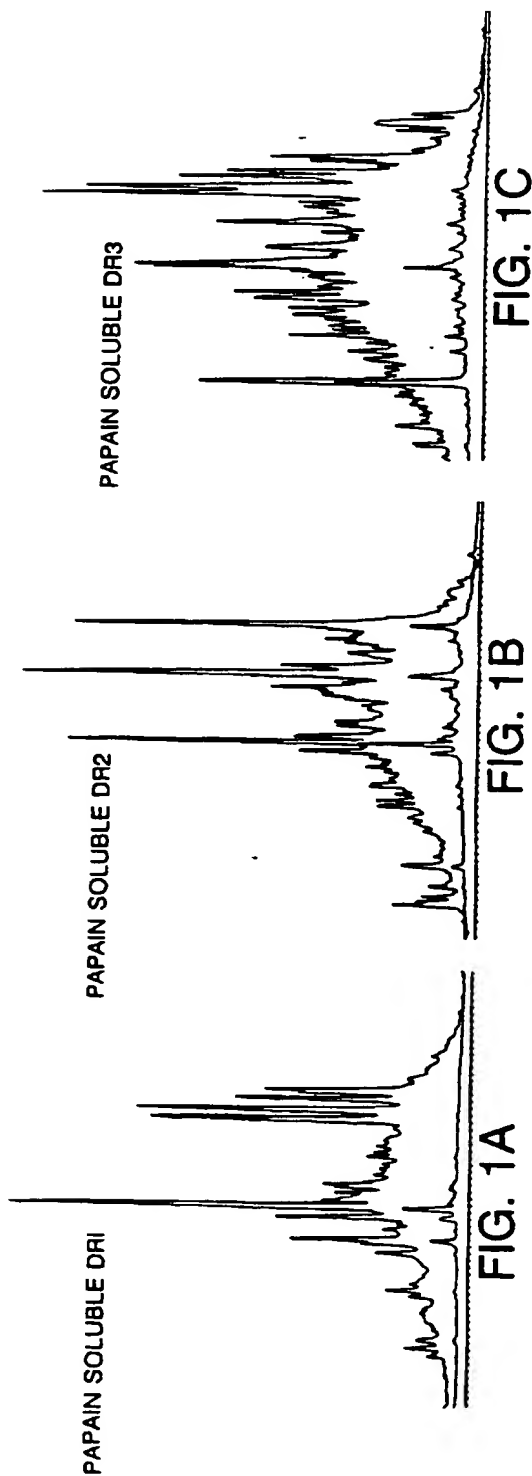
(b) eluting a mixture of peptides bound to said cell's first MHC allotype;

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(c) identifying a candidate peptid from said mixture, said candidate peptide being a fragment of a protein from said pathogen;

(d) testing whether said candidate peptide binds to a second MHC allotype, said binding being an indication that said candidate peptide is a nonallelically restricted immunostimulating peptide.

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2/3

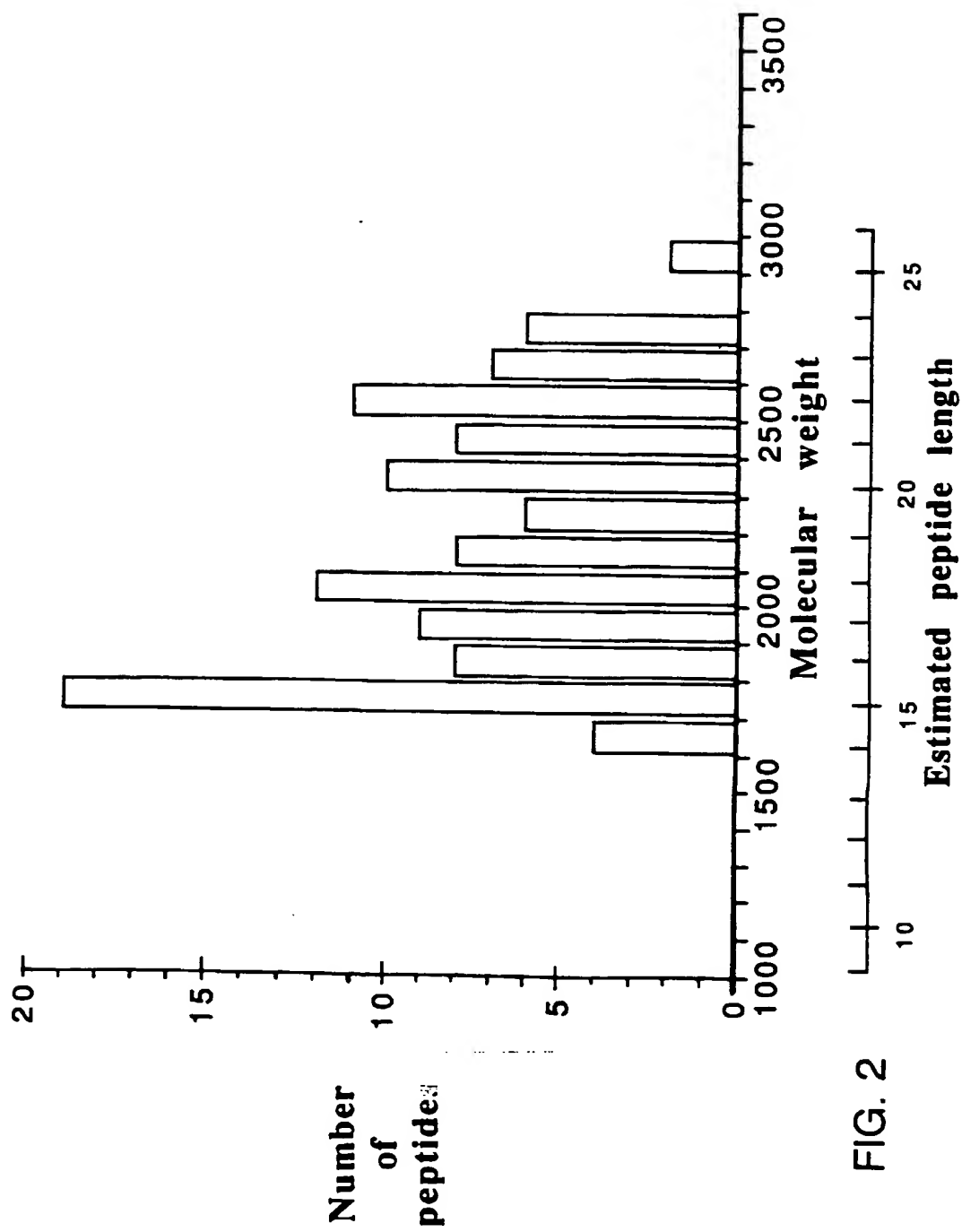


FIG. 2

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ATG GCC ATA AGT GGA GTC CCT GTG CTA GGA TTT TTC ATC ATA GCT  
 M A I S G V P V L G F F I I A  
 GTG CTG ATG AGC GCT CAG GAA TCA TGG GCT AAG ATG CGC ATG GCC  
 V L M S A Q E S W A K M R M A  
 ACC CCG CTG CTG ATG CAG GCG CTG CCC ATG TAA  
T P L L M Q A L P M stop

FIG. 3A

ATG GCC ATA AGT GGA GTC CCT GTG CTA GGA TTT TTC ATC ATA GCT  
 M A I S G V P V L G F F I I A  
 GTG CTG ATG AGC GCT CAG GAA TCA TGG GCT CTT CCC AAG CCT CCC  
 V L M S A Q E S W A L P K P P  
 AAG CCT GTG AGC AAG ATG CGC ATG GCC ACC CCG CTG CTG ATG CAG  
K P V S K M R M A T P L L M Q  
 GCG CTG CCC ATG TAA  
A L P M stop

FIG. 3B

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US93/07545

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(5) : A61K 37/00, 37/02, 37/22, 31/70; C07K 7/00, 7/08, 7/10; C07H 17/00

US CL : 530/300, 324, 325, 326, 327; 514/2, 44; 536/23.1; 424/450

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 530/300, 324, 325, 326, 327; 514/2, 44; 536/23.1; 424/450

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, Medline, Biosis, Chem Abs, Derwent WPI, Embase, search terms: peptide, MHC, class II, DR, I-A, I-E, liposome, iscom, self antigen, author names, antigen presentation, autoimmune

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Journal of Immunology, Volume 145, Number 6, Issued 15 September 1990, D.O. Sullivan et al., "Characterization of the specificity of peptide binding to four DR haplotypes", pages 1799-1808, see entire document.	1-18
Y	Immunology Today, Volume 12, Number 11, issued November 1991, A.M. Mowat et al., "ISCOMS - a novel strategy for mucosal immunization?", pages 383-385, see entire document.	11
Y	Immunology Today, Volume 11, issued January 1990, L. Adorini et al., "Peptide competition for antigen presentation", pages 21-24, see entire document.	1-18

☒ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

* Special categories of cited documents:	T	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be part of particular relevance	X	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier document published on or after the international filing date	Y	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	A	document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means		
"P" document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 07 October 1993	Date of mailing of the international search report NOV 03 1993
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer RON SCHWADRON <i>R. Schwadron</i>
Facsimile No. NOT APPLICABLE	Telephone No. (703) 308-0196

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US93/07545

## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Journal of Immunology, Volume 148, issued 01 June 1992, D.S. Collins et al., "Processing of exogenous liposome encapsulated antigens in vivo generates class I MHC-restricted T cell responses", pages 3336-3341, see entire document..	10